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COLPOMICROSCOPY: ITS VALUE IN THE MICROSCOPIC EXAMINATION OF THE UTERINE CERVICAL EPITHELIUM IN VIVO*

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IT IS the purpose of this paper to discuss the potentialities of the colpomicroscope as a means of supplementing cytology and histology in the study of benign cervical lesions and early carcinoma of the cervix in vivo.

The recent concentrated interest in the study and behavior of early cancers of the cervix and the so-called "precancerous" changes is an outgrowth of the concepts presented by Dubreuilh in 1896, d'Hotman de Villiers and Thérèse in the same year, Darier in 1908, Rubin in 1910, and others.

Thirty-three years ago Hinselmann[5] of Hamburg wrote on the possibilities of improving inspection of the vulva, vagina, and cervix. This started an era of increased interest in and intensive study of the cervix. The concept of studying the surface changes in the intact living cervix led to the development of the colposcope by Hinselmann in 1925. The colposcope, which should be distinguished from the colpomicroscope, is a binocular instrument magnifying 10 to 40 times, with which the cervix can be illuminated and inspected by direct vision. With these low magnifications, however, only the surface topography is visualized. Since the individual cells are not seen with the colposcope, the examiner is limited to inferring the probable cellular changes in the tissue from the colposcopic appearance of the surface. The limitations of such an examination are apparent.

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In an effort to study the living tissues of the cervix under magnifications high enough to visualize microscopically the surface cells and blood vessels, Pick[11] in 1934 wrote a paper on colpomicroscopy which he presented at the International Gynecological Congress in Holland, and constructed the first colpomicroscope magnifying 700 times. The instrument utilized incident-light external illumination first introduced in biology by Vonwiller[8] of Switzerland. Pick did not continue with his experiments. However, Antoine and Grunberger,[2] working along similar lines, developed a colpomicroscope in 1949 with broader application. Their instrument did not lend itself to photomicrography with standard color film available in this country. It was necessary for us to increase the brightness level of the illumination. This was accomplished with a special overvolting power supply. An increase in color temperature resulted from overvolting the light source but it did not affect the photomicrographs adversely.

The Colpomicroscope and Colpomicroscopic Examination

The colpomicroscope consists of a microscope with a built-in lamp, a guide tube, a microscope carrier with a bayonet fitting with a lock for the guide tube, and a stand (Fig. 1).

The microscope is a monocular instrument with a fixed 17.5 times coated achromatic objective. The interchangeable eyepieces range from 5 to 25 times, allowing magnifications from 87.5 to 437.5 times. The lamp housing is located at the top of the body of the microscope and contains a low-voltage incandescent bulb of 6 volts and 5 amperes (30 watts) which supplies the illumination for observation and photography. The lamp is connected to an intermediary regulating transformer with a built-in ammeter. Light is transmitted by means of mirrors and an optical system as a hollow cone, and brought to a focal point on the cervix, illuminating the surface and several layers of cells.

The guide tube is a hollow, metal cylinder, 11 cm. long and 3.2 cm. wide, closed at the front end by a glass plate. The back or open end locks into the bayonet fitting of the carrier. The guide tube houses and shields the long turret of the microscope containing the condenser and the objective, establishes an automatic coarse focal distance, and guides the mucous membrane of the portio adhering to the glass plate past the objective during coordinated scanning. A circle 8 mm. in diameter is engraved in the center of the glass plate of the guide tube. This circle indicates the area that can be scanned systematically with each application of the tube.

The microscope carrier supports the microscope proper on a sliding guide and is equipped with a lever and a drive screw for coordinated vertical and lateral movement of the guide tube. A bayonet lock firmly fixes the tube to the carrier. Sharp focusing is done with the micrometer screw at the ocular end of the carrier. Visual observation is possible below the surface of the epithelium, enabling one to examine several layers of the most superficial cells and the blood vessels.

The stand supports the microscope and the carrier. The carrier is attached by its vertical arm to the vertical arm of the stand by a long sliding guide. The stand may be attached by a jaw clamp to an examination table or to a floor support on casters. Two ball-and-socket joints on the supporting arms of the stand lock firmly by a single central knob in the middle of its horizontal arm and allow for easy manipulation of the instrument and for locking it in position.

Colpophotomicrography

Throughout this investigation a Kodak Retina camera 3C and a Retina microscope adapter model B with the microscope eyepiece were used. All photography was done with Kodachrome Professional Film, type A. The same principles of efficient illumination apply to photomicrography with the colpomicroscope as to photography with the ordinary microscope. It is essential to attain a high degree of definition and resolution in the image and to take full advantage of the filament brightness.

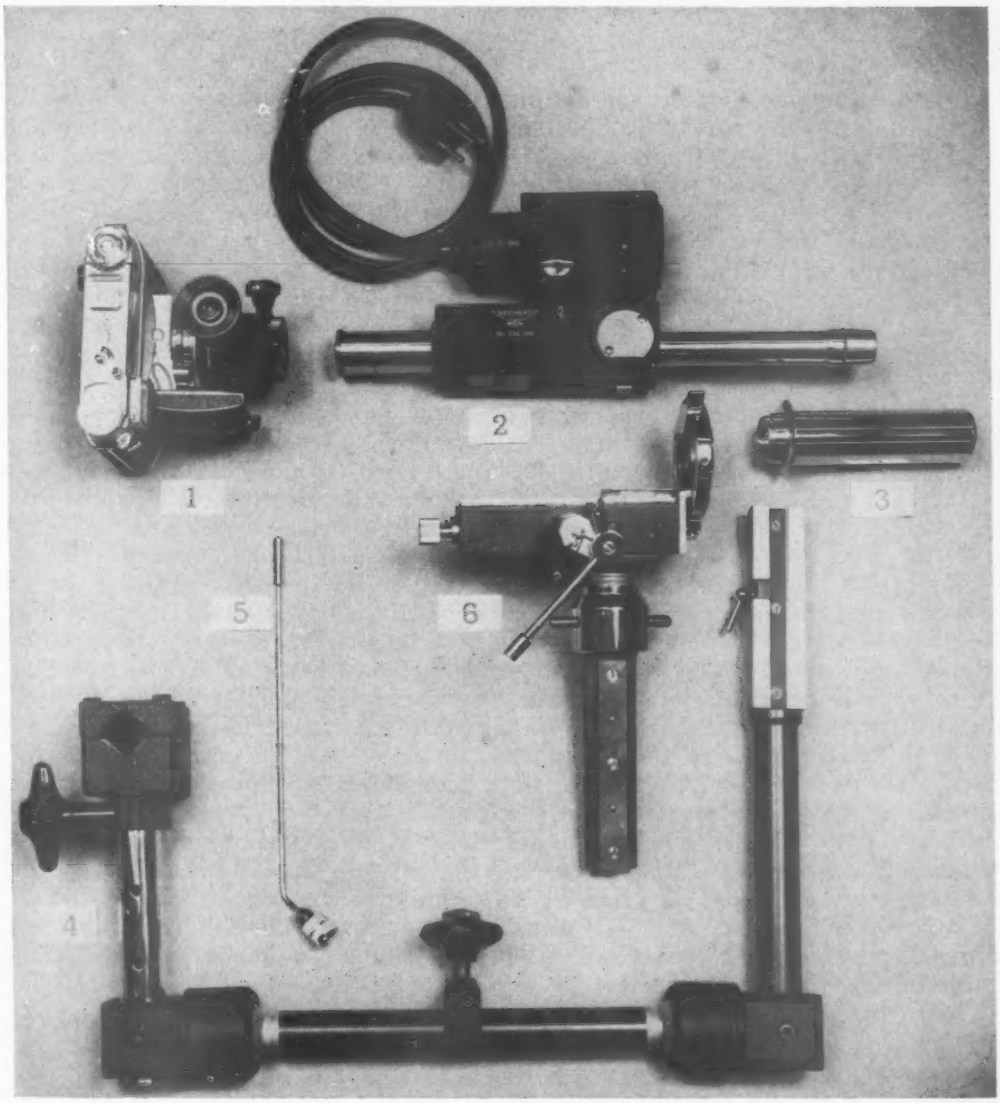

Fig. 1.—*1*, Kodak Retina camera with eyepiece adapter. *2*, Microscope with built-in lamp. *3*, Guide tube. *4*, Stand. *5*, Vaginal illuminator. *6*, Microscope carrier.

The light bulb of the microscope is of 6 volts and 5 amperes and emits 250 foot-candles of light for observation. For color photography, however, it is necessary to overvolt the lamp by 50 per cent. This is made possible by a special overvolting power supply in the regulating transformer. With this

arrangement a light output of 700 plus or minus 50 foot-candles is obtained. Exposure time varies from 2 to 5 seconds, being inversely dependent upon the intensity of staining of the cervix.

Technique of Colpomicroscopic Examination

Prior to the actual colpomicroscopic examination the patient is given one capsule of Nembu-Donna for sedation and to decrease the flow of cervical mucus. The patient is then examined bimanually to determine if colpomicroscopy is feasible. Blood, excessive mucus, vaginal atresia, fixed malposition of the cervix due to parametrial infiltration or scarring, marked papillary or nodular changes in the epithelial surface, and necrosis interfere with the examination. It is rare, however, that the examination cannot be conducted.

The colpomicroscopic examination is now begun. A bivalve speculum is introduced and the cervix brought into full view. If mucus is excessive and interferes with close apposition of the guide tube at the external os, the mucus plug may be removed with a cotton applicator dipped in a 2 or 3 per cent acetic acid solution. Excessive dabbing with the acid causes increased mucus secretion and epithelial damage with loss of cell detail. The procedure differs from colposcopy in that the cervix must first be stained. A cotton ball soaked in Mayer's hematoxylin solution is gently pressed against the portio. Care must be taken not to wipe or press too hard in order to avoid wrinkling or denudation of the epithelium and bleeding. Staining should continue for 3 to 5 minutes. Insufficient staining or overstaining interferes with the examination. It is therefore wise to inspect the cervix after 2 minutes to avoid overstaining. Any excess stain is then completely removed from the vagina and the posterior fornix by gentle dabbing with a cotton ball. If the surface of the cervix is too wet it will slip away from the guide tube. If, however, the surface is not moist enough air bubbles will form between the epithelium and the glass plate and interfere with vision. Experience teaches the optimum moisture for the cervix. The speculum is then removed and the vagina is opened with right-angle retractors by separating the anterior and posterior vaginal walls. The exposed cervix may now be moistened with normal saline or dried as needed. The guide tube, rinsed in warm water, dried, and then wiped with 70 per cent alcohol by weight and redried, or immersed in aqueous Zephiran solution 1:1,000 for 45 minutes and then rinsed in warm water and dried, is introduced into the vagina between the two retractors so that the glass plate is in perfect apposition with the surface of the cervix. It is important to center the region to be examined in the small circle engraved on the glass plate of the guide tube. A long vaginal illuminator introduced through the guide tube helps in orientation and in the selection of the site for examination. Only the zone circumscribed by this circle is accessible to the microscopic examination. It is advisable to select an area for examination in which normal and pathologic tissues adjoin. The abnormal epithelium stains darker than the normal.

The guide tube is next attached to the carrier on the stand and locked in the bayonet fitting. This automatically places the tube firmly in position. After it is locked, a check should be made of the site-circle relationship with the use of the vaginal illuminator. The retractors are not removed from the vagina. They may be carefully tilted to move the cervix to bring other areas of epithelium into view. It is generally preferable to insert the instrument afresh for inspection of new regions.

The microscope proper is next slipped into the guide tube along the sliding guide on the upper surface of the carrier and secured to the carrier by a

setscrew on the left. The whole apparatus is now a firmly mounted system with the microscope in perfect coaxial attachment. Observation is begun after the light is turned on at the transformer. The microscope is in coarse focus automatically when in proper apposition. Sharp focusing is done with the micrometer screw at the ocular end of the carrier and then the entire zone is systematically scanned with the lever and screw which move the guide tube vertically and laterally through coordinated movements.

When the examination is completed the microscope proper is first unlocked and removed, leaving the guide tube and carrier in place. The carrier is next unlocked from the guide tube and swung aside. The guide tube is then withdrawn from the vagina, and finally the retractors, at which time any excess stain may be gently swabbed from the vagina.

Material

The description of the colpomicroscopic findings is based on the study of the cervices in 165 selected cases. The majority of these cervices were normal or showed benign atypias. Eleven of the cases were cancers of the portio and all were positive colpomicroscopically. In every instance the Papanicolaou smear and the Schiller test were done. When the findings were either equivocal or positive, biopsies were taken. The area selected for biopsy was immediately marked with India ink. During colpomicroscopy photomicrographs were taken of all cervix cancers and of many of the noncancerous cervices.

Colpomicroscopic Observations (Figs. 2 to 5)

The normal squamous epithelium when viewed through the colpomicroscope appears as flat, polygonal cells. The cells are distributed evenly and their boundaries are generally discernible. The cytoplasm is usually pale and may contain small, fine, dark granules. The cytoplasm as a result of overstaining, degeneration, or inflammation may be deeply stained. The nuclei are darkly stained and not crowded. They are pyknotic or vesicular and vary in size depending upon the stage in the cycle, the presence of inflammation, and the menopausal status. The epithelium varies in thickness and when the superficial layers of epithelium are thinned out intermediate cells are seen. Exfoliated single cells or plaques may be superimposed upon intact epithelium. These areas then stain darker and the cells are more numerous. Single, free, rolled cells appear rodlike and may float about. The epithelium may fold and crease forming straight, deeply stained striae across the field. This is due to flattening of the epithelium of the normally convex surface of the cervix. Rarely the epithelium resembles epithelial pearls. These formations in normal epithelium are interpreted as a heaping up of the epithelium in papillary arrangement. Scattered single or clumped polymorphonuclear leukocytes, lymphocytes, and nuclear fragments may be deposited on the large epithelial cells. Strands of mucus appear as clear, glistening bands across the field.

The columnar epithelial cells are smaller than squamous cells and when seen on end they appear in honeycomb formation and have little cytoplasm. The nuclei are small, dark, round or oval, vary little in size, and are crowded. Because of the crowding of the nuclei the columnar epithelium gives the impression of being deeply stained. Occasionally the epithelium is seen laterally. Then the nuclei appear closely packed and resemble a school of minnows.

If the columnar epithelium is denuded the underlying stroma is visible. Stromal cell borders are not well defined. The nuclei are indistinct, stain

paler than those of the columnar cells, are vesicular, unevenly distributed, more crowded than the nuclei of the flat epithelium, yet not as closely packed as those of columnar cells.

Here and there a gland opening is seen. Gland openings are oval and filled with clear mucus or mucus containing leukocytes, lymphocytes, and cellular debris. The margins of the gland orifices are surrounded by densely packed, small, dark nuclei of the columnar cells and varying numbers of leukocytes and debris in close proximity to the gland openings. Atypia of the cells about the lumina of the glands is seen in epidermidization. These atypical cells resemble squamous cells, exhibit changes in size and shape, and their nuclei vary in staining intensity. Such cells are interpreted as actively growing reparative squamous cells.

In a true erosion there is a complete loss of the squamous epithelium exposing a base of connective tissue within which scattered nuclear particles and inflammatory cell infiltrates are seen. Normal squamous epithelium adjoins the denuded area. In the papillary pseudo-erosions the summits of the overgrowths of epithelium are seen as ringlets of crowded, dark, columnar cells surrounding nests of indistinctly outlined connective tissue stroma and leukocytes. The glandular pseudo-erosions exhibit glands imbedded in an inflammatory stromal environment.

In epidermidization, irregular intermingling of squamous and columnar cells is seen wherein squamous cells outline, invade, and replace papilloglandular areas of columnar cells. The squamous cells often show considerable atypia but lack the marked pleomorphism and polychromasia of the malignant cells. They represent actively growing cells regenerating in an inflammatory environment. The nuclei of the columnar cells may be large, crowded onto each other, and deeply stained. A gland opening within the squamous epithelium of a healing glandular pseudo-erosion appears like a rim from which mucus mixed with inflammatory cells and debris exudes.

Leukoplakia is not very impressive when viewed through the colpomicroscope. In hyperkeratosis a clear homogeneous structureless area is seen corresponding to an area of keratinization. Rarely such a clear structureless area may represent a loss of superficial squamous epithelium without visualization of the unstained deeper bare structures. At times very faint nuclear outlines with perinuclear halos are observed. In parakeratosis the nuclei are widely separated, small or pin-point, and deeply stained. The cytoplasmic outlines are indistinct or absent and cellular detail is lacking.

The small blood vessels and capillaries are best observed in the unstained cervix but can also be seen in the stained cervix. The blood vessels appear as a mosaic network of regular, delicate or fairly coarse loops and strands against a pinkish homogeneous background. The large blood vessels have an orange-red hue and the blood cells course through them and the capillaries. Most of the vessels are parallel to the surface. When perpendicular they are seen as loops which appear much darker. Under normal conditions the capillary vessels vary little in size and are of small caliber. They are regular in arrangement and uniformly distributed. In disease increased vascularity and irregular distortion of the vessels are seen. The capillaries are more numerous, abnormally widened and lengthened. The loops exhibit finer coiling. In erosions moderate vascular hyperplasia and hypertrophy are noted and in malignancy, especially, the arrangement of the vessels is bizarre and the deviation from normal is most intense. Telangiectasis of the cervix is visible to the naked eye, nothing being added by the colpomicroscope except magnification of a dilated vascular network.

Fig. 2.

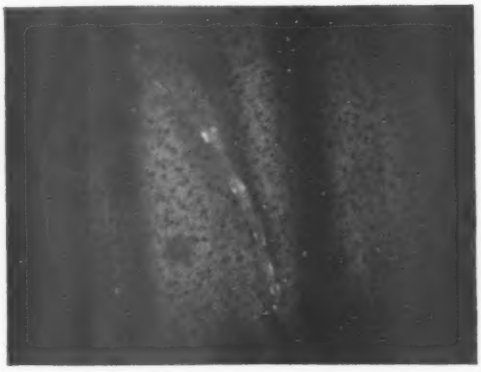

Fig. 3.

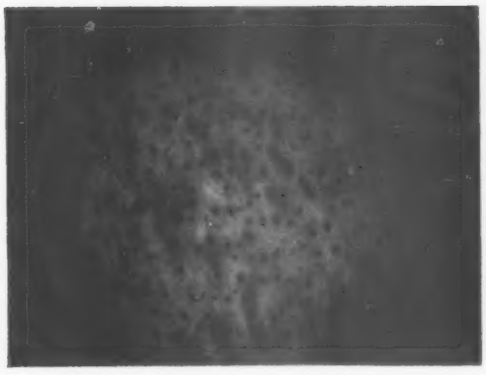

Fig. 4.

Fig. 5.

Fig. 2.—Normal squamous epithelium with two dark epithelial folds and a strand of clear mucus between them. (Original magnification ×175.)

Fig. 3.—Normal squamous epithelium 14 days following x-irradiation showing cell outlines, increase in cell size, nuclear enlargement, and vacuolation. (Original magnification ×175.)

Fig. 4.—Squamous epithelium with leukoplakia to the left and intraepithelial carcinoma to the right. (Original magnification ×175.)

Fig. 5.—Normal creased squamous epithelium below and to the right separated by an oblique line from squamous carcinoma above and to the left. (Original magnification ×175.)

The malignant changes in the epithelium are striking. The entire surface may show the neoplastic change, the cells being densely packed, scattered singly or in small groups. Isolated multilobular or multinucleated single, large, dark cells may be distributed at random in an environment of normal or somewhat swollen epithelium. A sharp line of demarcation may separate the malignant cells from the normal epithelium. Whorls of cancer cells indicative of pearl formation occur. Areas of superficial necrosis and inflammatory cell infiltrates are seen, especially in the more advanced lesions.

The evaluation with the colpomicroscope is based on abnormalities of the cells of the uppermost layers. The epithelial changes seen have all the cytologic criteria of malignancy except invasion. It should be remembered that the old cardinal principle that cancer is necessarily invasive is abandoned in the diagnosis of in situ carcinoma. Both pleomorphism and polychromasia must be present to the degree seen in malignancy. Attention is devoted to the character of the nuclei and the cells and their relationship to each other, but the cytologic changes rather than the architectural arrangement are the more important in the colpomicroscopic evaluation of the malignant change. Increase in cell size, crowding, and bizarre cell shapes are seen. The cell borders may or may not be distinct and the orderly arrangement of normal epithelium is disturbed. Abnormal chromatin patterns are conspicuous. There is variation in nuclear size and depth of staining; distorted nuclei; multinucleation; occasionally a multinucleated giant cell; vacuolation and a rare mitotic figure. The nuclear-cytoplasmic ratio is disturbed in favor of the nuclei.

General Comment

There is no conflict or rivalry between colpomicroscopy, cytology, and biopsy, as each method has its own advantages and complements the others. Colpomicroscopy is a microclinical method which permits repeated intensive inspection and observation of the cervix without disturbing the epithelium or causing undue discomfort. Permanent photomicrographic records can be made upon which to base future review, study, and teaching. These recorded observations and photomicrographs can be compared with the prior Papanicolaou smears, thus broadening the knowledge of both the cytologist and the colpomicroscopist. Where tissue examination does not confirm a lesion which has exfoliated abnormal cells, the colpomicroscope may help locate the abnormality of the epithelium. The colpomicroscope also provides a means of selecting specific areas for biopsy.

Although a colpomicroscopic examination of the cervix may be performed in approximately 20 minutes, it must be emphasized that the technique demands training and experience in handling the instrument and in the interpretation of the findings.

Since only the superficial layers are visualized colpomicroscopically, nothing can be said concerning the changes in the depth of the epithelium. Therefore, the technique should not be attempted in frank or advanced lesions where necrosis would prevent accurate surface visualization, but should be performed in those cases where the cervix appears normal or presents only a minimal lesion. If no other means but the eye were used, the presence of necrosis is suspicious enough to lead to a biopsy and thus detection. When there are definite cellular abnormalities the colpomicroscopic evaluation is

readily made. It is the borderline nature of cellular changes which makes the evaluation more difficult. Benign atypias of the cervical epithelium seen in inflammatory and regenerative processes, as well as those indicative of interchange at the squamocolumnar junction, often cause confusion in the interpretation even though polychromasia and pleomorphism are variable and not present to the degree ordinarily seen in malignancy.

The ever-present possibility of the false negative impression applies to the colpomicroscopic method just as it applies to other methods of tissue evaluation. Significantly, an overlying keratinization, the so-called "spray carcinoma" of Schiller, and lesions which are entirely endocervical will in all probability escape detection by the colpomicroscopists.

Although the colpomicroscope was originally intended to be a single-purpose instrument, it may also be applied in:

1. Periodic examinations of the cervix in pregnancy.
2. Hormone evaluation and cyclic changes of the squamous epithelium.
3. Observation of changes in the tissues associated with recurrence of lesions.
4. Study of epithelial changes following treatment with hormones, steroids, and chemicals.
5. Prognostic evaluation of the radiation and postradiation changes in the epithelium.
6. Studies of the blood vessels and the circulation.
7. Hematologic studies.
8. Cell genetics.
9. Examination of the mouth cavity and pharyngeal walls.
10. Examination of dermatoses.
11. Animal and plant research.

Summary and Conclusion

The principles and technique of colpomicroscopy have been discussed. The cervices of 165 selected patients were studied by this method. Eleven of these cervices exhibited proved cancers of the portio and the remaining 154 were normal or showed benign atypical changes of the cervical epithelium. The colpomicroscopic findings of the normal, atypical, and malignant cervices have been discussed and the changes or lack of changes leading to confusing impressions or false negative interpretations have not been overlooked.

It is felt that colpomicroscopy is a valid procedure worthy of recognition in the clinical and research study of the cervix and an important accessory which should prove highly effective in the study of the behavior of borderline lesions and early carcinomas of the cervix.

It is hoped that these findings may stimulate others to undertake colpomicroscopy and so contribute further to a technique which perhaps may change our concepts regarding the present methods of examination of the epithelium of the cervix.

I wish to thank Mr. I. E. Chase, Jr., of Eastman Kodak Company for his valuable suggestions and technical aid with the lighting and the color photomicrographs and to express appreciation for the willing cooperation given me during this study by Wm. J. Hacker and Co., New York, N. Y.

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SARCOMA BOTRYOIDES

Report of Two Cases

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THE term "sarcoma botryoides" is applied to mesodermal mixed tumors of the lower genitourinary tract. The word botryoid in Greek means "like a bunch of grapes," and refers to the peculiar characteristics of this type of neoplasm which looks like grapelike masses. In males it originates in the bladder, urethra, and prostate; in females in the cervix, vaginal vault, and occasionally in the bladder. It is a comparatively rare tumor. Among 26,114 gynecologic admissions to the Charity Hospital, New Orleans, only 21 cases of botryoides sarcoma were recorded according to Sternberg and associates.[5] Dwyer[1] reported only one case among 4,000 gynecologic admissions. It occurs predominantly in children. McFarland[3] collected reports of 74 cases, all of them occurring in patients less than 22 years old. Forty-two of these cases were in children of 2 years of age or younger. The tumor, which actually arises in the Müllerian duct, is relatively rare in the male. This may be explained by the fact that the tube disappears at an early developmental stage in boys. The botryoides sarcoma progresses rapidly, invading the adjacent viscera and the bladder. Its usual course is repeated recurrence and death from obstruction of the urinary passage. No authentic cures were confirmed by McFarland[3] in his collected cases. Isolated cases reported since his review were all fatal.[1, 2, 6] The recent paper by Ober and Edgcomb,[4] based on a search of the world literature, revealed only one case in which a 5 year survival following operation had been achieved. In another case, reported by Frick,[3] in which the patient was living and well 10 years after two operative removals of the tumor, the botryoid tumor was situated upon the posterior vaginal wall.

CASE 1.—F. T., a 26-year-old unmarried white woman, whose menstrual history had been normal until February, 1949, began to have intermenstrual bleeding accompanied by a yellowish discharge. She had been seen by her family physician, who prescribed local therapy. Since this did not control the symptoms, the patient was referred to us.

On her first visit in April, 1949, she had lost no weight and had no other symptoms than the intermenstrual bleeding and discharge. On examination, a large polypoid mass involving the vault of the vagina and the cervix was found. The tumor measured approximately 8 cm. in diameter, and bled readily upon palpation. There did not appear to be any intra-abdominal extension or fixation of the tumor. Roentgenogram of the chest was negative. On biopsy, the tumor was noted to be a mesodermal mixed tumor of the cervix.

The patient was admitted to the hospital and an abdominal total hysterectomy and partial vaginectomy were performed. Severe bleeding was encountered, requiring replacement of 1,500 c.c. of blood. The tumor mass measured approximately 10 cm. in its greatest diameter and involved the vault of the vagina as well as the cervix (Fig. 1).

The patient's postoperative course was uneventful except for jaundice, due to hemolysis, which cleared rapidly. Since operation, the patient has remained well without any evidence of recurrence. She was last seen in December, 1957, at which time she was in good health.

Review of the pathologic material confirmed the diagnosis of sarcoma botryoides (Fig. 2).

Comment.—In this case of sarcoma botryoides, a survival of over 8 years was achieved by an abdominal total hysterectomy and partial vaginectomy.

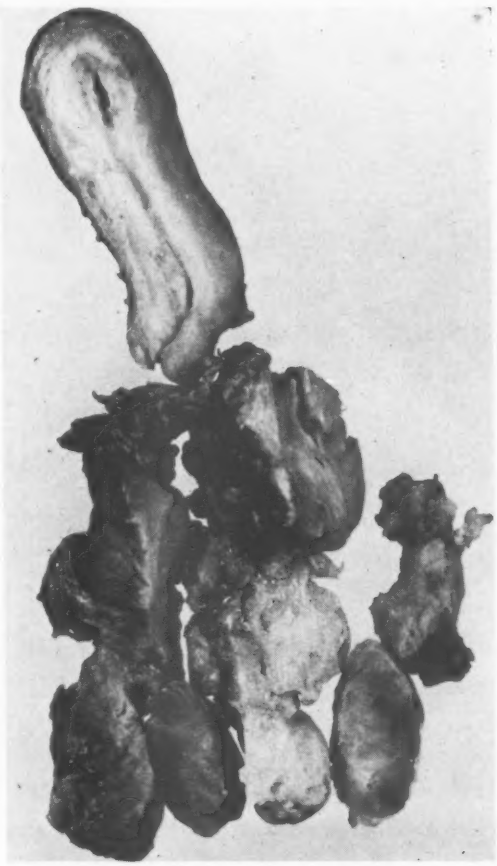

Fig. 1.—Case 1. Gross specimen showing size of tumor in relation to the uterus.

CASE 2.—This patient was a white girl, 18 years old. At the age of 5 years, she had fallen out of a second-story window and fractured the mandible and skull. She had no trouble from this or any other illness until she developed persistent vaginal bleeding about 3 weeks before she sought medical attention. On examination this was found to be due to a tumor protruding from the cervical os. Biopsy showed it to be a sarcoma botryoides.

Examination disclosed a young girl in excellent general health; the only findings were a grapelike tumor protruding from the cervix and extending into the vault of the vagina. It did not appear to invade the bladder or the rectum.

The patient was admitted in January of 1956 and a panhysterectomy was carried out with a partial node dissection; the ovaries were preserved. The patient did well until May,

1956, when she was examined and a large abdominal mass was disclosed. Laparotomy revealed sarcomatosis involving the entire abdomen. The major portion of the tumor was scooped out. This measured approximately 30 by 22 by 7 cm. in its greatest dimensions. The omentum was removed and the peritoneal cavity lavaged and the wound closed without drainage. The patient was then given x-ray therapy to each of four abdominal quadrants, receiving 2,100 r in each, with the use of 250 kv. at 30 Ma., with 1½ mm. of copper filter at 70 cm. target-skin distance. Patient was given Oreton intramuscularly every week. In July, a paracentesis was done which removed 3,200 c.c. of bloody fluid.

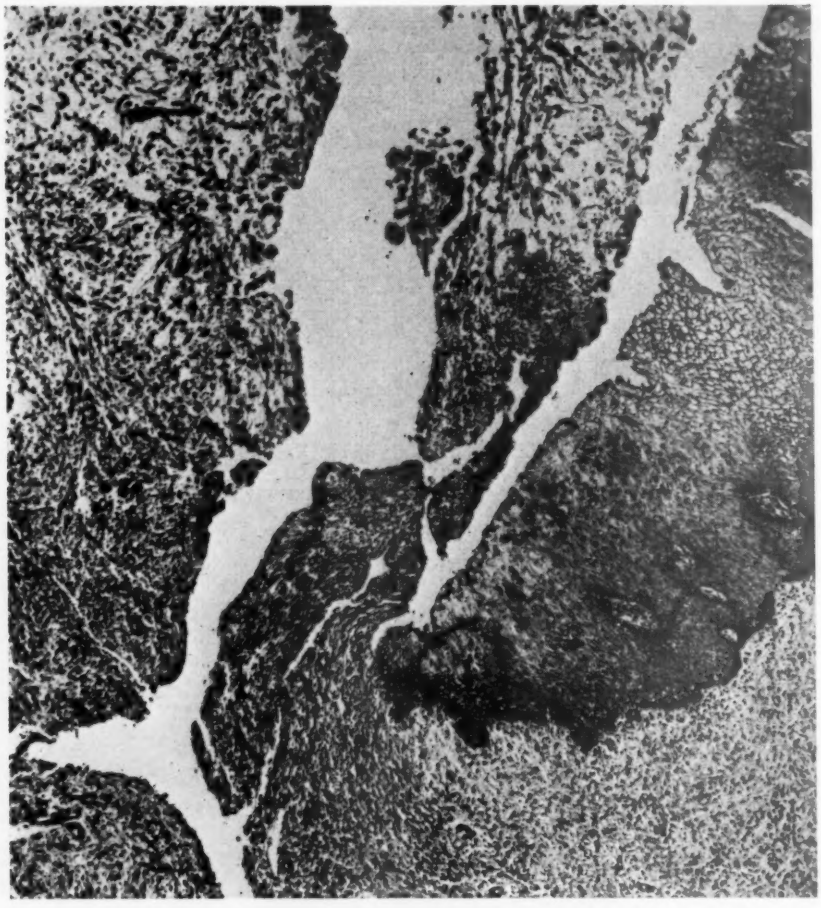

Fig. 2. Case 1. High-power photomicrograph of the tumor.

On Aug. 16, 1956, the patient died of inanition with great abdominal distention. The chest film remained clear throughout.

Comment.—In this case of a fast-progressing sarcoma botryoides, a panhysterectomy failed to prevent the fatal outcome of the disease.

Summary

Two cases of sarcoma botryoides are reported.

In one case of sarcoma botryoides, in a 26-year-old woman, an abdominal total hysterectomy and partial vaginectomy resulted in an 8 year survival of the patient.

In the second case, in an 18-year-old girl, a panhysterectomy failed to prevent abdominal sarcomatosis and fatal outcome of the disease.

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RADIOGRAPHIC FEATURES OF RECTOSIGMOID ENDOMETRIOSIS

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THE condition referred to as endometriosis is not uncommon in gynecologic practice. Through several routes, endometrium can invade or become implanted upon practically every pelvic organ and more rarely upon extrapelvic organs.

Colcock and Lamphier,[3] in a review of 213 patients with endometriosis who underwent exploratory operations, found 18.3 per cent to have endometriosis of the rectum, rectosigmoid, sigmoid, or small intestine. Kratzer and Salvati[8] reported that there was some degree of bowel involvement in 34.22 per cent of the 225 cases in their review. Javert[7] stated that benign endometrial cells are capable of dissemination and metastasis along the same pathways followed by endometrial adenocarcinoma. By direct extension or by lymphatic spread to adjacent serosal surfaces, the endometrial cells can become implanted upon the intestines. Because of their close proximity, the rectum and rectosigmoid colon are the most frequently involved segments (70 to 80 per cent of the reported cases). However, many cases of involvement of the small intestines and of the appendix have also been reported.[3, 11]

Although endometriosis does occur in both early and late life, approximately 75 per cent of cases occur between 30 and 50 years of age. Involvement of the rectosigmoid may be present without obstruction. In approximately 50 per cent, however, there will be some clinical evidence of obstruction. There is a high incidence of sterility associated with endometriosis, the percentage in the literature varying from 40 to 60 per cent. Of 14 patients with endometriosis of the intestines seen at the Leahy Clinic from 1940 to 1950, 8 were childless, 5 had 1 child, and 1 was single.[3]

Common symptoms of endometriosis of the rectosigmoid colon are:

1. Menorrhagia and metrorrhagia
2. Dyspareunia
3. Pain in the rectum caused by the passage of stool, usually only at menses, or at least intensified at that time.
4. Symptoms of low-grade obstruction such as nausea, crampy pains, and constipation, which are more apt to occur during the menstrual period.
5. Extension of the menstrual backache to the thighs and legs.
6. A history of acquired dysmenorrhea appearing in a multipara, or a change in the type of pain of the dysmenorrhea of the multipara.
7. Unexplained sterility. This has not been true of the cases in this report as only 1 out of 6 married women was childless.

8. Recurrent diarrhea frequently coincident with the menstrual period without rectal bleeding. From review of the literature and the standpoint of logic this should be true. It is of interest to note, however, that in 4 of our 7 cases rectal bleeding was the presenting complaint. Berlin and Finestone[2] have reported a case of rectosigmoid endometriosis with bloody diarrhea and normal menses.

9. Fairly good general health without weight loss.

Sigmoidoscopy shows only narrowing of the affected area. Ballon, Strean, and Simon[1] were able to make the diagnosis of obstructive ulcerating endometriosis of the rectum by proctoscopic biopsy. Obviously, if the lesion is beyond the reach of the sigmoidoscope, no abnormalties will be noted. The only way to make a preoperative diagnosis then is by radiographic examination of the colon.

The x-ray findings of rectosigmoid endometriosis by barium enema can be classified into two groups, constricting and nonconstricting lesions. Implants on portions of the bowel which are freely suspended by a mesentery are less likely to become constricting lesions than are implants upon portions of the bowel which are partially extraperitoneal and more firmly attached.

Two factors influence partial obstruction and hence the x-ray findings: first the endometrial tumor may compromise the lumen of the bowel; and, second, the associated inflammatory reaction may produce active spasm and later constricting and fixing fibrosis. This late cicatricial contracture in some cases is the principal basis of the x-ray findings.

In *constricting lesions* the following radiographic changes are noted:

1. Annular narrowing of variable length, usually relatively short, with or without an associated filling defect caused by the endometrial tumor. Most frequently the narrowing tends to be eccentric, as can be noted in the illustrations.
2. The area of involvement is sharply demarcated.
3. The lesions are usually fixed and tender when palpated under fluoroscopic observation.
4. *Most important* is the fact that the mucosal folds are intact through the lesions.

In *nonconstricting endometriosis* the findings are different:

1. A submucosal tumor is demonstrated with normal mucosa overlying and surrounding the lesion.
2. The extraluminal extent of the lesion may produce varying degrees of displacement of the bowel as can be noted in several of the cases reported in this paper.
3. A localized spastic and irritable segment of bowel is seen above and below the lesion.
4. Under fluoroscopic control the lesions are locally tender.
5. The variation in size of the tumor depending on the phase of the menstrual cycle may be extremely helpful in establishing a diagnosis. This was well illustrated by a case presented in a previous article.[4]

The differential diagnosis would include, mainly, primary colon carcinoma, diverticulitis, and secondary involvement of the colon by pelvic tumors and inflammatory masses.

Carcinoma of the colon arises from the mucosa and destroys its normal pattern. Therefore the presence of a normal mucous membrane pattern is the one most important x-ray feature that differentiates endometriosis from carcinoma of the colon. There could be a remote possibility of malignant degeneration in an endometrial implant which would, of course, confuse this differential point. Sampson[9] stated that "external endometriosis probably has the same potential

for malignant change as normally located endometrium.'' Scott[10] reported 2 cases of ovarian adenocarcinoma which had histologic features that accorded with Sampson's criteria for malignant degeneration of endometrial implants. No cases of malignant endometriosis of the colon have yet been reported, however.

In diverticulitis, the diverticula are easily demonstrated and there is marked associated spasm extending well above and below the region of actual involvement. The lesion itself is usually long and the irregular, jagged, saw-toothed margins are quite characteristic of diverticulitis. Perforation, with formation of a pericolic mass, can complicate the picture and make the differential diagnosis more difficult.

When primary pelvic tumors actually invade the wall of the colon, the x-ray findings can simulate those of rectosigmoid endometriosis. Of great importance in the differential is the finding of the soft tissue mass of the pelvic tumor on the plain film.

The necessity of differential diagnosis of rectosigmoid endometriosis from the more rare primary large bowel tumors, such as lipoma, leiomyoma, fibroma, and mesenteric cysts, seldom arises and is mentioned only for completeness.

Fig. 1.—Case 1. Full-sized film shows the location of the lesion just above the rectosigmoid junction. The inserted pressure spot film demonstrates the characteristic eccentric narrowing referred to in the text. Note the normal mucosal pattern through the involved area.

Case Reports

CASE 1.—This was a 40-year-old married white woman, gravida ii, para ii, who gave a history of crampy lower abdominal pain, diarrhea, and rectal bleeding during each menstrual period for many years. The menses were normal.

The physical examination was essentially negative. All laboratory tests were negative except for occasional occult blood in the stools.

A barium enema disclosed an area of narrowing in the sigmoid colon, appearing to lie just above the peritoneal reflection. The defect was somewhat eccentric, the major involvement being at the inferior aspect of the sigmoid in this area. The mucosal pattern was not disturbed and there was no indication of ulceration. It was thought that the findings were highly suggestive of involvement of the sigmoid colon by endometriosis.

At operation, many chocolate cysts were found on the surfaces of the pelvic organs and in the omentum. Two lesions were noted involving the sigmoid colon. One was at the mid-sigmoid area, while the second was just above the peritoneal reflection and was thought to be the one which had been demonstrated by the barium enema. Resection was deemed unwise. Biopsies of the sigmoid lesions were carried out and surgical castration was performed.

The pathologic report of the sigmoid biopsies was typical endometriosis with evidence of old and recent hemorrhages.

CASE 2.—This was a 45-year-old single white woman, who gave a history of lower abdominal pain and discomfort radiating to the back for the past 3 or 4 years. This was intensified by bowel movements and by urination. There were no systemic complaints and the menstrual history was normal.

Physical examination disclosed slight suprapubic tenderness. Pelvic and rectal examinations showed tenderness and induration, in the form of nodulations, in the left cul-de-sac, and there was a suggestion of an orange-sized mass in the right adnexa.

A barium enema disclosed narrowing of the low sigmoid for an area about 1½ inches in length. This seemed to be the result of infiltration of the submucosal wall. The overlying mucosa was normal. There was the impression of an extraluminal mass observed from above. A radiographic diagnosis of sigmoid endometriosis was suggested.

Fig. 2.—Case 2. Oblique spot film of the sigmoid lesion demonstrates its submucosal character. Arrows indicate the direction of extrinsic pressure.

At operation an orange-sized chocolate cyst was found firmly adherent to the mesentery of the sigmoid and involving the sigmoid colon immediately adjacent. There were multiple small hemorrhagic cysts in the right ovary. Hysterectomy, bilateral oophorectomy, and salpingectomy were performed. The sigmoid lesion was then resected and end-to-end anastomosis was carried out.

The pathologic report of the resected lesion of the colon was typical endometriosis with localized hemosiderosis involving the serosa and muscular coats. The submucosa and mucosa were intact.

CASE 3.—This was a 40-year-old married white woman, gravida ii, para ii. For 2 years she had complained of abdominal bloating and constipation during the first 3 days of her menstrual period. There were lower abdominal cramps associated with bowel movements. Otherwise the menses were normal.

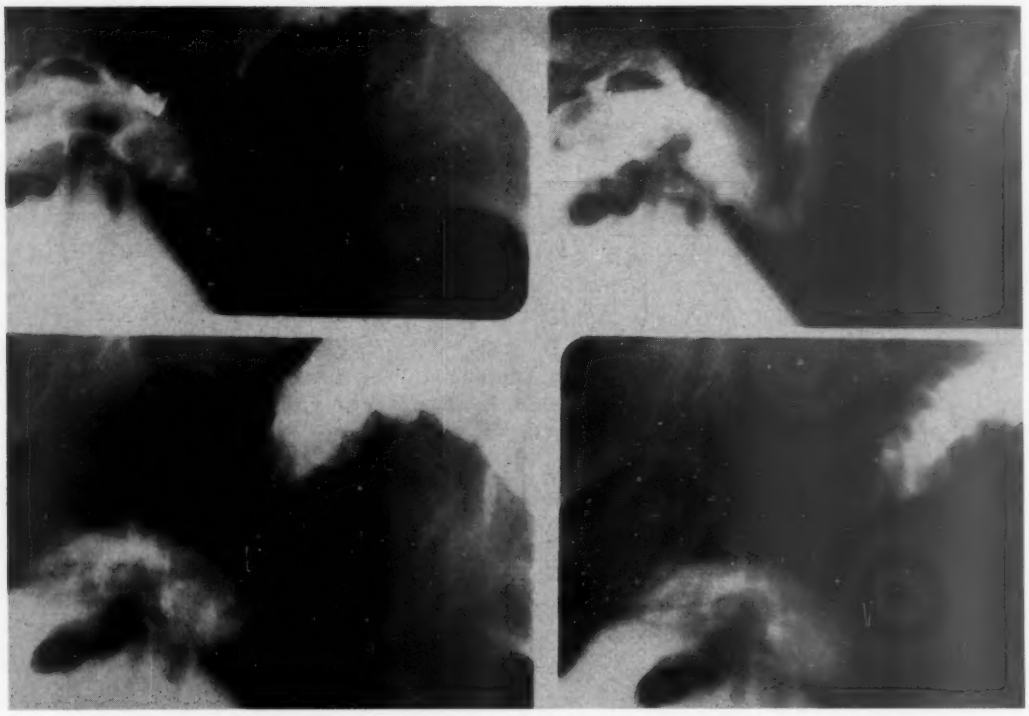

Fig. 3.—Case 3. Spot films of the sigmoid colon show the narrowed segment with normal mucosa. The element of associated spasm is evidenced by variations in caliber of the sigmoid lumen on different films.

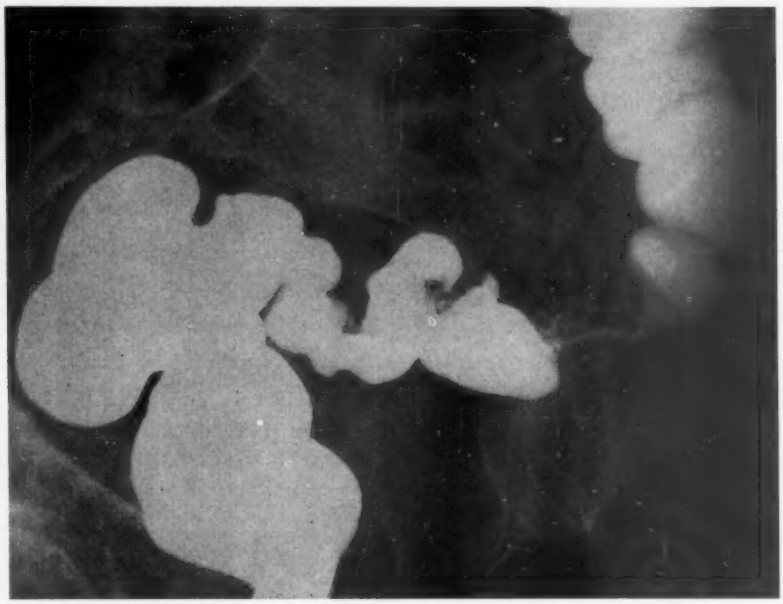

Fig. 4.—Case 4. Narrowing of the sigmoid with accentuation of the mucosal fold pattern, secondary to the submucosal tumor.

Pelvic examination showed lemon-sized masses arising from each ovary. The remainder of the physical examination was negative.

A barium enema disclosed moderate narrowing of the mid-sigmoid colon which was the result of involvement of this segment by an extrinsic submucosal mass involving the bowel wall. This was interpreted as a pelvic tumor mass with sigmoid involvement, and endometriosis was suggested.

Fig. 5.—Case 5. Eccentric narrowing of the sigmoid with very obvious pressure effect from below as indicated by arrows. The mucosa through the narrowing is normal.

Fig. 6.—Case 5. Opened surgical specimen showing the intramural, submucosal location of the tumor.

Laparotomy disclosed an endometrial cyst arising from each ovary. That on the left was firmly adherent to the sigmoid colon and required sharp dissection for removal. There was, in addition, a similar mass at the ileocecal junction, which was not removed. Both ovaries were removed but no bowel resection was carried out.

The pathologic report was endometriotic cysts of both ovaries.

CASE 4.—This was a 57-year-old married white nulligravid woman whose only complaint was intermittent rectal bleeding for 2 months. There was no associated change in bowel habits, nor was there any complaint of pain. The menopause had followed bilateral oophorectomy and salpingectomy at the age of 34.

The physical examination was noncontributory.

A barium enema showed an area of narrowing of the sigmoid at about its junction with the descending colon. The narrowing was distinctly submucosal with the fold pattern appearing somewhat accentuated, as is frequently encountered in submucosal infiltrative disease. The radiographic interpretation was tumor of the sigmoid wall in a submucosal location.

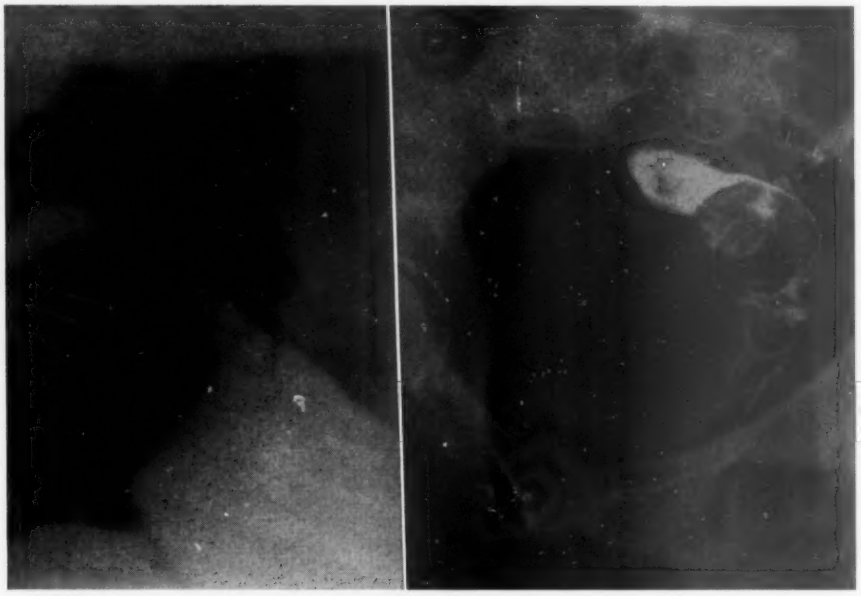

Fig. 7.—Case 6. Spot films of the sigmoid lesion in both oblique projections. Again the characteristic eccentric narrowing is evident.

Exploratory operation disclosed a tumor involving the wall of the sigmoid in its upper portion. The sigmoid was opened and explored and it was noted that the lesion was completely submucosal. The tumor was dissected free and the colotomy was repaired.

The pathologic report of the removed tumor was typical endometriosis with endometrial glands and a considerable amount of stroma.

CASE 5.—The patient was a 64-year-old married white woman, gravida i, para i. Her only complaint was increasing constipation for the 6 months prior to admission. Prior to that time her bowel habits were normal. There was no history of melena or diarrhea. She had gone through an apparently normal menopause about 20 years previously.

Physical examination revealed a walnut-sized, movable, nontender mass in the left lower quadrant. Pelvic and rectal examinations were negative.

A barium enema showed a concave defect along the inferior border of the mid-sigmoid colon which produced some narrowing of the lumen but was nonobstructive. The findings were interpreted as the result of an extrinsic mass involving the bowel wall but without intraluminal extension.

At operation, a lesion infiltrating the wall was noted in the sigmoid colon about 5 cm. above the peritoneal reflection. It extended from the left broad ligament and the left ovary, and was adherent to the latter. The ovary was removed. The sigmoid colon was

opened and probed with a finger, which revealed that the lesion impinged upon the lumen but the overlying mucous membrane was intact. An anterior resection of the sigmoid colon was carried out.

The surgical specimen showed hypertrophic musculature with numerous glands of endometrial type. There was also some endometrial stroma present. The diagnosis was endometriosis of the sigmoid colon.

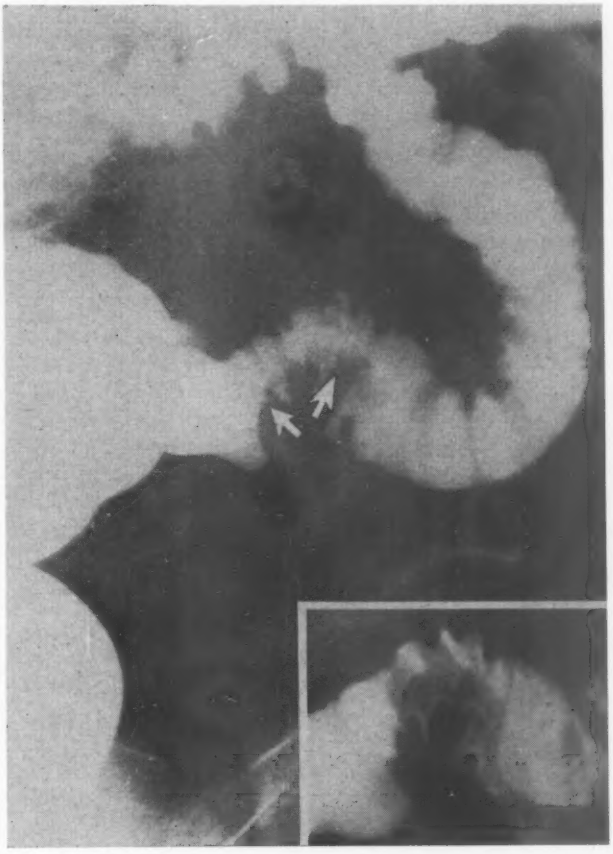

Fig. 8.—Case 7. Full film of the rectosigmoid area and inserted spot film of the lesion. Arrows indicate the mass at the inferior wall. The diverticula led to the misinterpretation of a pericolic inflammatory mass. Note the normal mucosal pattern overlying the mass.

CASE 6.—This patient was a 42-year-old married white woman, gravida iv, para iv. The patient's menses had been normal up to 5 years prior to admission. At that time she developed dysmenorrhea which increased in severity. Seven months prior to admission she developed severe abdominal cramps with each menstrual period with associated bloody diarrhea. This would subside with the cessation of menses.

The physical examination was negative except for pelvic and rectal examinations. These disclosed fulness in the right adnexal region and there was a firm mass palpable behind the lower uterine segment extending from left to right. Sigmoidoscopy showed at 10 cm. a protrusion on the anterior wall of the sigmoid, interpreted as the result of the extrinsic mass. There was no break in the mucous membrane.

A barium enema revealed a filling defect in the low sigmoid colon producing considerable narrowing of the lumen. The defect was smooth in outline and did not appear to distort the mucosal pattern. This was interpreted as a tumor involving the sigmoid wall lying in submucosal location. The diagnosis of endometriosis was suggested.

Exploratory operation revealed cystic ovaries which contained chocolate material. There was a mass involving the low sigmoid colon which measured 6 cm. in length and 3½ cm. in diameter. This was biopsied but not removed. Total hysterectomy, bilateral oophorectomy, and salpingectomy were performed.

The pathologic sections of the sigmoid lesion revealed the typical changes of endometriosis.

CASE 7.—This patient was 47 years old, married, white, gravida iii, para iii. The patient was seen by her physician because of bright red rectal bleeding accompanying her last two menstrual periods. Twelve years previously, she had had rectal bleeding not associated with the menses. This was corrected by hemorrhoidectomy without recurrence. There was no diarrhea or pain associated with her present rectal bleeding.

Physical examination and sigmoidoscopy were negative.

A barium enema showed a localized area of narrowing at the junction of the proximal and middle thirds of the sigmoid colon. There were several diverticula evident in this region. The extent of the involvement of the lumen was 5 cm. and there was extrinsic pressure from below on this segment. The interpretation was probable pericolitis with an inflammatory mass secondary to local diverticulitis.

At operation a resection of a sigmoid was carried out for a sigmoid tumor. There was no other pelvic abnormality.

The pathologic report was endometrial implant on the wall of the sigmoid colon.

Summary and Conclusions

1. Seven cases of endometriosis of the rectosigmoid have been presented.

2. The radiographic findings have been described.

3. These findings are sufficiently characteristic that, when combined with the clinical data, a correct diagnosis should be possible in most cases.

4. It is of interest to note that, in the present 7 cases, and in the 2 previously reported,[4] only one of the 8 married women gave an indication of sterility.

5. Contrary to the impression gained from a review of the literature, rectal bleeding was a presenting complaint in 4 of our 7 cases.

We wish to thank Dr. Kenneth Seagraves for allowing us to add his case (No. 7) to this series.

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FULL-THICKNESS ANTERIOR COLPORRHAPHY FOR CORRECTION OF URINARY STRESS INCONTINENCE*

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URINARY continence in the female is dependent on the integrity of the posterior urethrovesical angle. This has been clearly indicated by the work of Jeffcoate[1] and Hodgkinson[2] with the use of cystograms.

They have shown that:

A. Stress incontinence results when this angle is increased to 180 degrees or more, as in the voiding state; and that

B. Stress incontinence is overcome when this angle can be maintained at less than 180 degrees when the patient is not voiding.

The Marchetti[3] test indicates that support at the bladder neck which re-establishes the retropubic vaginal angle overcomes stress incontinence. The retropubic vaginal angle is therefore the external counterpart of the posterior urethrovesical angle seen in lateral cystograms.

The monumental work of Goff,[4] Ricci and Thom,[5] and Koster[6] proved histologically that no fascia is present between the vagina and bladder, between vagina and rectum, or between vagina and urethra. To repeat their work, sections have been taken which include all tissues from the lumen of the vagina to the lumen of the neighboring organ (Figs. 1 to 6). These show that an avascular cleavage plane filled with loose areolar tissue occurs between the bladder and vagina and between the rectum and vagina. They also show that there is no line of demarcation between the urethra and vagina, the musculatures being intimately fused.

The retropubic vaginal angle can be re-established by a simple vaginal plastic procedure which utilizes the full thickness of the vagina. This corrects urinary stress incontinence.

Procedure

The anterior vaginal wall is divided between Allis clamps at a point just beyond the fusion of vagina and cervix. This incision opens immediately into the avascular cleavage plane between bladder and vagina (Fig. 7).

The full thickness of the upper edge of the incision is grasped with Allis clamps on either side of the midline. The assistants make downward traction on the Allis clamps. The entire thickness of the anterior vaginal wall is

*Presented at a meeting of the Philadelphia Obstetrical Society, Dec. 5, 1957.

Fig. 1.

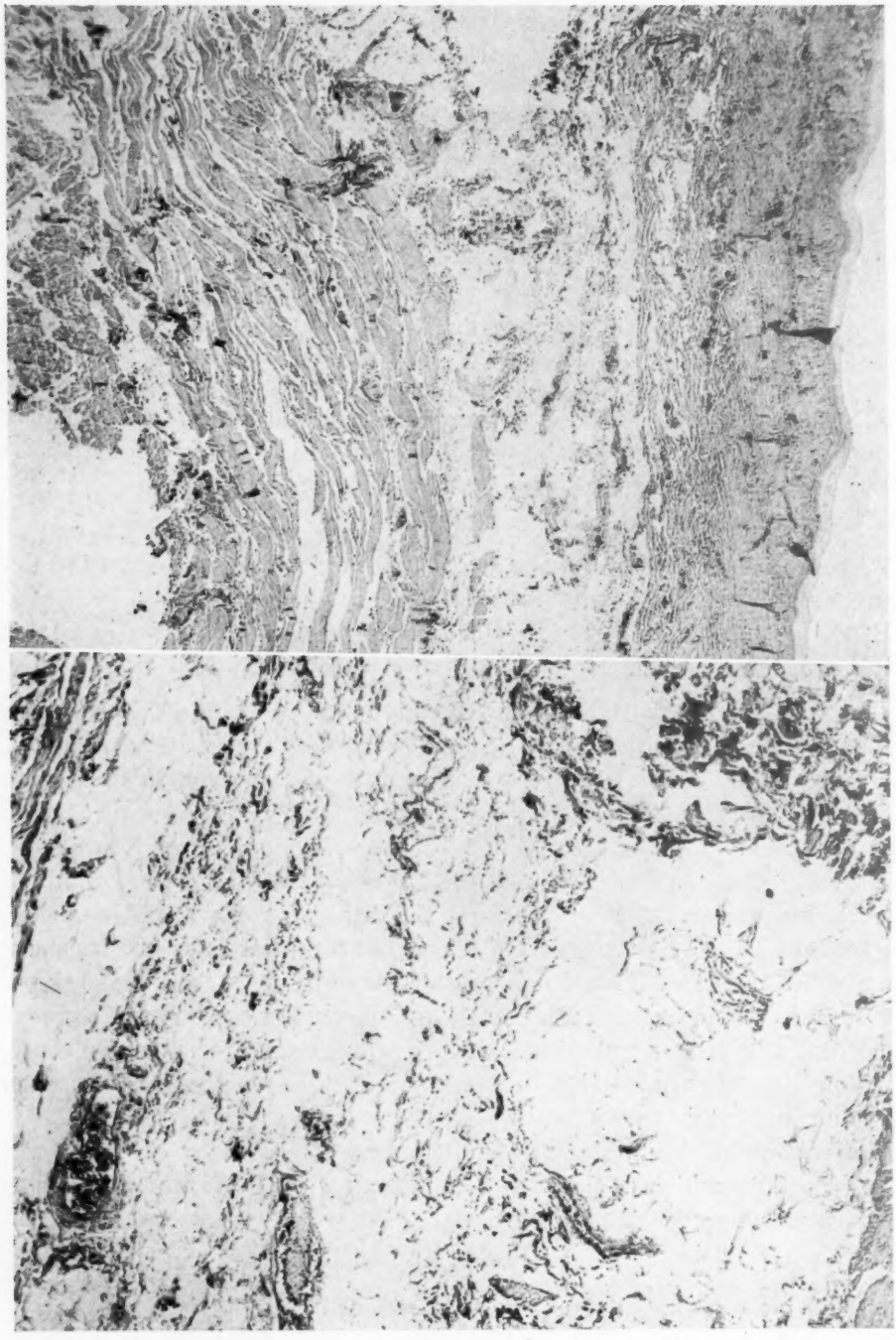

Fig. 2.

Fig. 1.—Low-power photomicrograph of section including all tissues from mucosa of bladder (left) to vaginal mucosa (right). The cleavage plane is clearly visible between muscularis of bladder on left and muscularis of vagina on right. (×7.2.)

Fig. 2.—High-power magnification of vesicovaginal area showing that cleavage plane contains loose areolar tissue principally. (×30.)

Fig. 3.

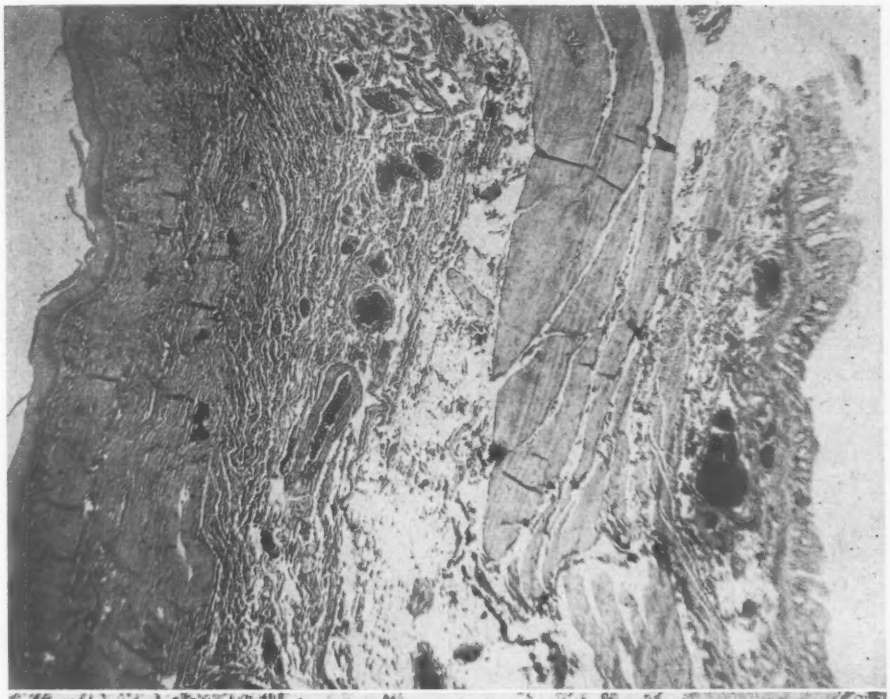

Fig. 4.

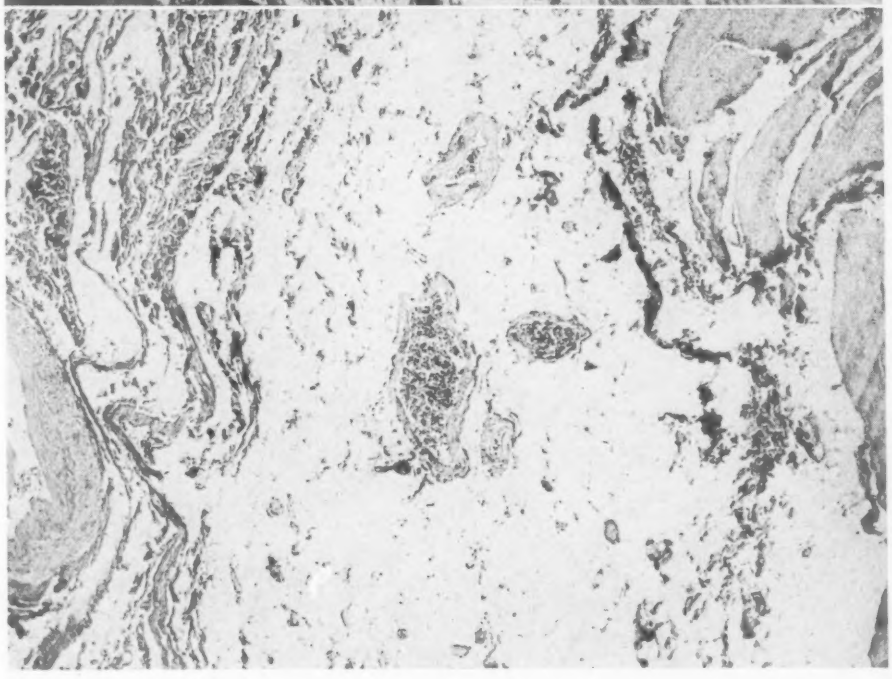

Fig. 3.—Low-power photomicrograph of section including all tissues from mucosa of vagina (left) to mucosa of rectum (right). The cleavage plane is clearly visible between muscularis of vagina (on left) and muscularis of rectum (on right). (×14.5.)

Fig. 4.—High-power photomicrograph of rectovaginal area showing that cleavage plane contains loose areolar tissue principally. Blood vessels are of capillary size. (×30.)

Fig. 5.

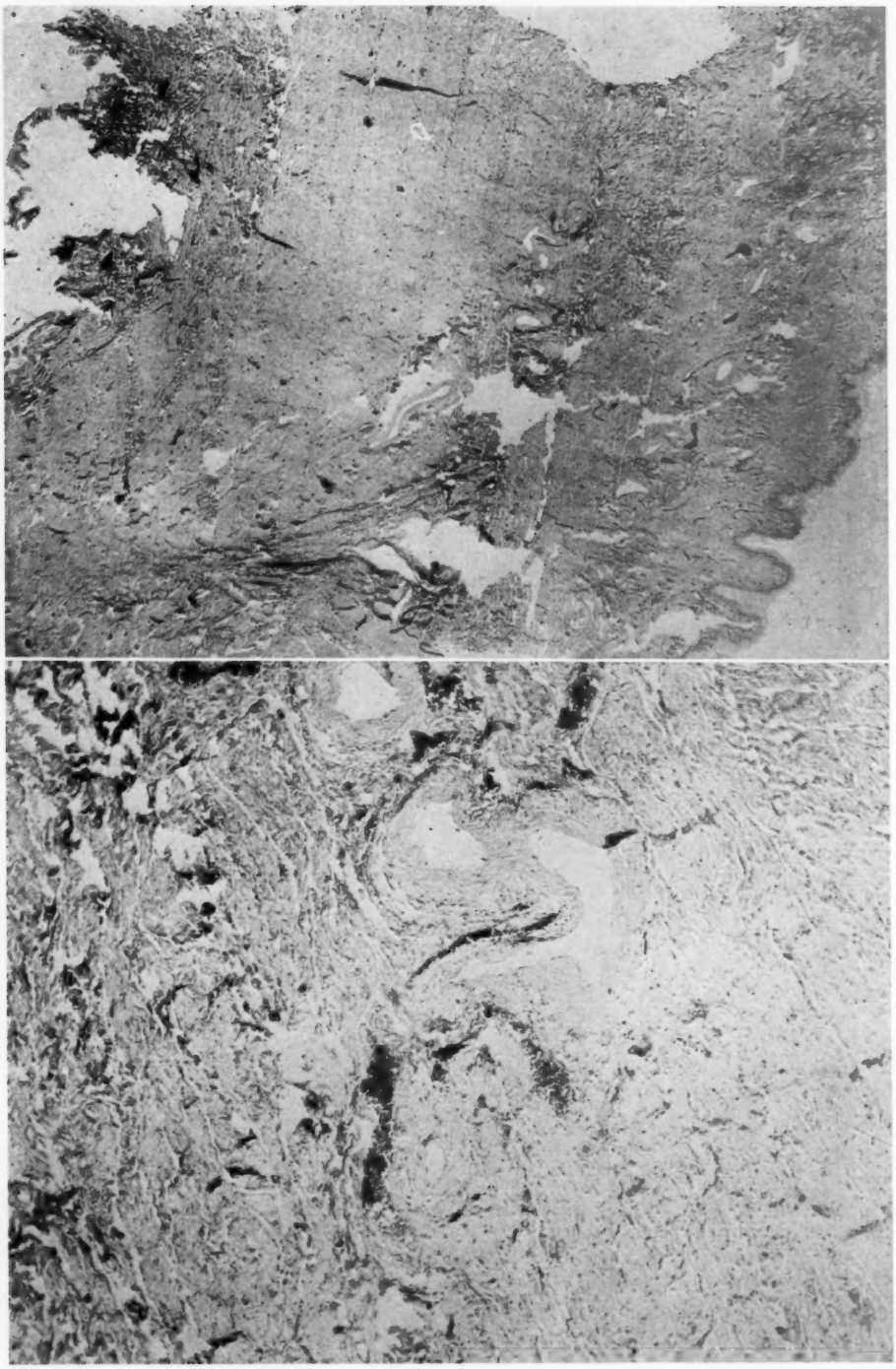

Fig. 6.

Fig. 5.—Low-power photomicrograph of section including all tissues from mucosa of vagina (right) to mucosa of urethra (left). No cleavage plane is visible nor is there any fascia present. (×5.5.)

Fig. 6.—High-power photomicrograph of urethrovaginal area showing solid muscle without demarcation between muscularis of vagina and urethra.

divided in the midline by a vertical incision with straight scissors. The incision extends the full length of the cleavage plane which ends at the fusion of urethra and vagina.

This point is usually 3 to 4 cm. below the urinary meatus.

Bleeding during this stage occurs from the cut edges. The blood emerges between mucosa and muscularis. Bleeding is easily controlled by the application of Allis clamps (Fig. 8).

The anterior vaginal wall is freed laterally and superiorly from the bladder by sharp scissors dissection so that the widest possible area of redundant vaginal wall may be excised.

This wide excision is the key to the re-establishment of the retropubic vaginal angle. Superiorly the excision takes approximately the form of a double Roman arch, when all freed vaginal wall has been resected (Fig. 9).

Enough vaginal wall is excised so that side-to-side approximation cannot be accomplished. This is tested, in the upper third with Allis clamps. If enough vaginal wall has been removed, the tips of the clamps will not meet in the midline (Fig. 10).

The tested areas of vaginal wall can be brought together behind the symphysis if the tips of the Allis clamps are directed upward, just as is done in the Marchetti test (Fig. 11).

As the full thickness of the anterior vaginal wall is approximated, the interrupted sutures are drawn upward by the elasticity of the tissues of the vaginal wall. They disappear from view behind the symphysis. Only the last placed suture can be seen as the assistant pulls down the suture ends to facilitate the placing of the next suture.

As the closure continues toward the cervix, the edges may be too easily approximated. If this happens, additional arched segments of vaginal wall must be excised.

The full thickness of the cut vaginal wall must be held securely by Allis clamps throughout the procedure until the sutures are placed. If this is not done, the muscularis retracts laterally so that sutures are placed in mucosa alone and the purpose of the operation is defeated (Fig. 12).

The upward retraction of successive sutures indicates that the "retropubic vaginal" angle has been restored to less than 180 degrees and simultaneously the posterior urethrovesical angle has now been reduced to less than 180 degrees. This accomplishes by vaginal operation the mechanical advantage produced by the Marshall-Marchetti operation (Fig. 13).

Technical Considerations

A word of warning is indicated. This procedure permits no compromise between methods. Closure under moderate tension results from the wide excision of relaxed vaginal wall. Only the full thickness of the vaginal wall retains sufficient tensile strength to allow this type of closure. Therefore, separation of the vaginal mucosa from its muscularis for the purpose of "developing" a fascia must be avoided. A wide excision of mucosa alone will result in a large defect extremely difficult to close.

The musculature of the urethra is intimately fused with that of the vagina. This relationship cannot be improved surgically, therefore we avoid dissection beyond the point of fusion of urethra and vagina.

Since there is no abnormality in the bladder or urethra responsible for stress incontinence, it is not necessary to plicate the bladder or urethra or to use Kelly and cystopexy sutures.

Fig. 7. Fig. 8.

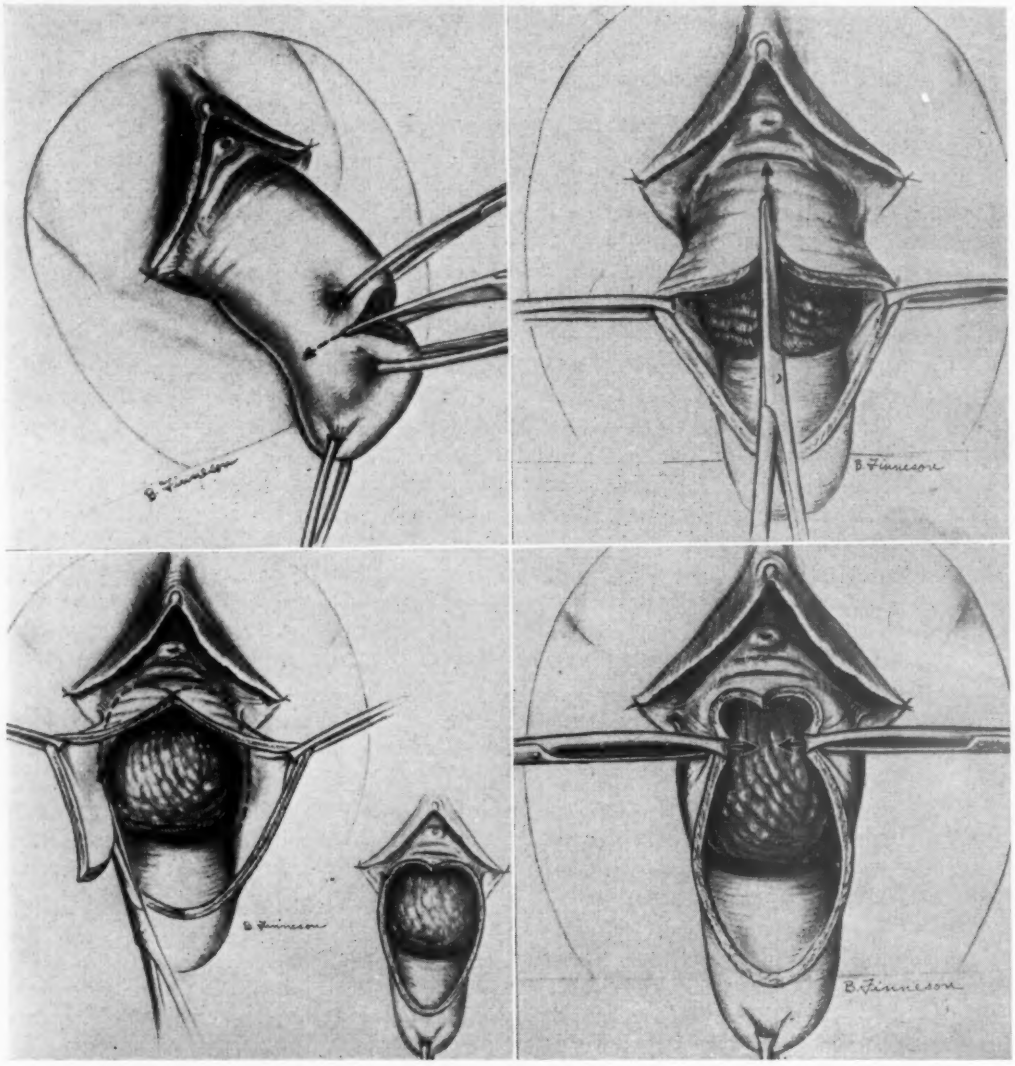

Fig. 9. Fig. 10.

Fig. 7.—The anterior vaginal wall is divided between Allis clamps at a point just beyond the fusion of vagina and cervix. This incision opens immediately into the avascular cleavage plane between bladder and vagina.

Fig. 8.—The full thickness of the upper edge of the incision is grasped with Allis clamps on either side of the midline. The assistants make downward traction on the Allis clamps. The entire thickness of the anterior vaginal wall is divided in the midline by a vertical incision with straight scissors. The incision extends the full length of the cleavage plane which ends at the fusion of urethra and vagina.

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Fig. 10.—Enough vaginal wall is excised so that side-to-side approximation cannot be accomplished. This is tested, in the upper third, with Allis clamps. If enough vaginal wall has been removed, the tips of the clamps will not meet in the midline.

Fig. 11. Fig. 12.

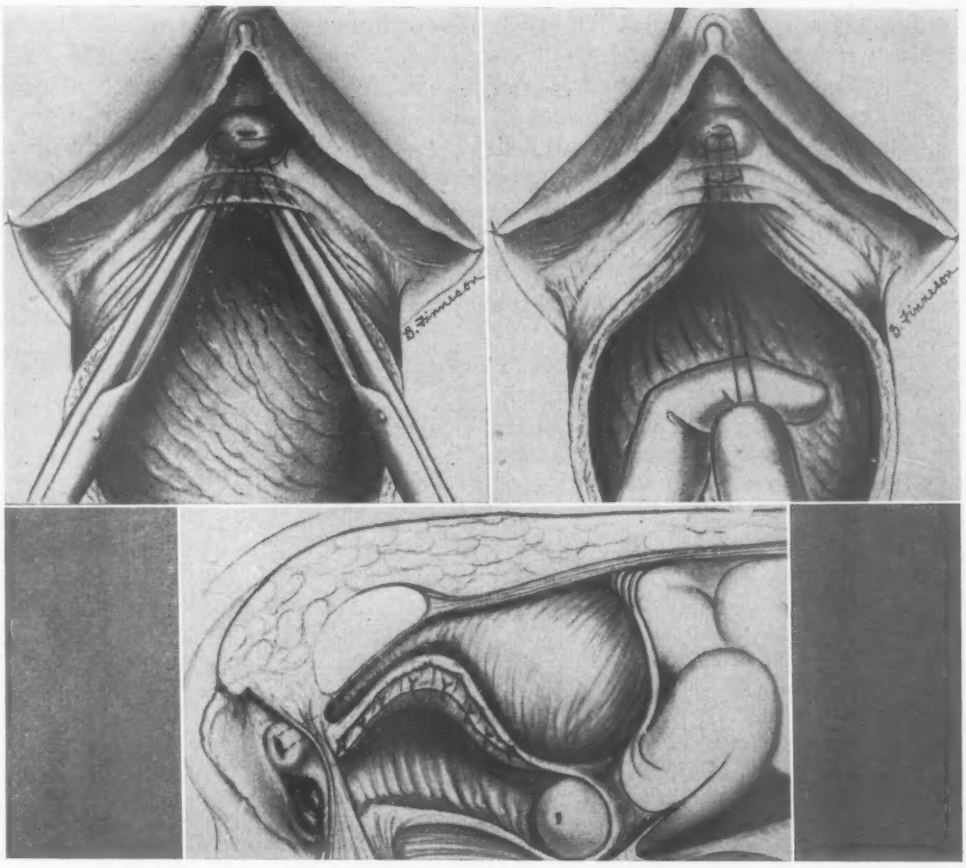

Fig. 13.

Fig. 11.—The tested areas of vaginal wall can be brought together behind the symphysis if the tips of the Allis clamps are directed upward, just as is done in the Marchetti test.

Fig. 12.—As the full thickness of the anterior vaginal wall is approximated, the interrupted sutures are drawn upward by the elasticity of the tissues of the vaginal wall, and disappear from view behind the symphysis. Only the last placed suture can be seen as the assistant pulls down the suture ends to facilitate the placing of the next suture.

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Fig. 13.—The upward retraction of successive sutures indicates that the "retropubic vaginal" angle has been restored to less than 180 degrees and simultaneously the posterior urethrovesical angle has now been reduced to less than 180 degrees. This accomplishes by vaginal operation the mechanical advantage produced by the Marshall-Marchetti operation.

Selection of Patients

Patients with stress incontinence and a loss of retropubic vaginal angle are tested according to the Marchetti technique. The patients who exhibit a favorable response to the test are considered good candidates for this operation just as they would be for the Marshall-Marchetti procedure.

This vaginal operation, in addition, is now routinely used for anterior colporrhaphy even if stress incontinence is absent. It also can be used with other vaginal procedures, such as the Manchester operation, or vaginal hysterectomy.

Results

Twenty-seven patients with stress incontinence have been treated by this method with uniformly good results.

These patients have been followed from 6 months to 5 years. The results in our hands are superior to those of previous vaginal plastic operations.

Three patients (11 per cent) have developed asymptomatic recurrent cystoceles. These occurred among the early cases in the series when the excision was too conservative.

Advantages of This Method

1. There is minimal blood loss because the cleavage plane is relatively avascular.

2. The intimate blood supply of the flaps is preserved. This tends to insure a stronger more flexible vagina.

3. Urologic injuries are avoided because the surgeon's vision is not obscured by a layer of vaginal muscularis covering the bladder and ureters. Only the vaginal edges are sutured and these are in view at all times during the suturing.

4. Patients have uneventful postoperative convalescence. Distortion of the bladder and urethra is avoided. As a result, the Foley catheter is removed after 24 hours and patients can usually void within the next 24 hour period. Residual urine is rarely more than 20 or 30 c.c. Early ambulation is encouraged. Patients are immediately aware of their newly acquired continence.

Conclusion

A simple vaginal plastic procedure has been described in which the full thickness of the anterior vaginal wall is used to re-establish the retropubic vaginal angle. This corrects pre-existing urinary stress incontinence.

Twenty-seven cases are reported.

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Discussion

DR. FRED B. NUGENT.—Any plastic procedure which results in 100 per cent control of stress incontinence of urine with only 10 per cent of recurrence of cystocele is a good one and while the author's series is small, the results thus far have been most encouraging. The Roman arch type of dissection and repair is a new concept and on the basis of Dr. Frankel's experience a sound one.

Stress incontinence of urine is a symptom which can be caused by many defects. Dr. Frankel's very careful criteria in the selection of patients for this operation should be followed implicitly. Of equal importance is his series of "don'ts." Let no one be deceived, the excellent results reported bespeak a nicety of judgment on Dr. Frankel's part in distributing the tensions evenly over the suture line. While the technique is simple it requires great skill on the part of the surgeon.

I find myself in disagreement with the essayist on two counts. First, it is difficult for me to believe that the support of the bladder neck and the urethra depends on the full thickness of the vaginal wall alone. Second, the method of repair outlined may well utilize fully other structures to which no reference is made in the text.

During my resident years, the celebrated argument between Byron Goff and Lillian K. P. Farrar over the presence of useful supporting structures in the vaginal walls was in full swing. In considering the merits of this difference of opinion I went to Webster's Dictionary. It states: "Fascia—a sheet or layer of more or less condensed connective tissue covering, supporting, or binding together internal parts or structures of the body." This concept must be separated clearly from that of aponeurosis.

The excellent photomicrographs we have seen show the bursalike potential space between the bladder and vaginal walls. Such a space is desirable between two neighboring organs whose content may vary tremendously at various times. The transverse sections shown in Dr. Ullery's classic monograph on stress incontinence are familiar to most of you. They clearly demonstrate the areolar supporting tissues which carry in the blood supply, nerves, and fibrous tissue. The median raphe is practically devoid of these structures.

Gynoplastic procedures have been designed around the use of these tissues since pelvic surgery began. Mengert's classic experiment clearly demonstrated that they really do support. He attached weights to a tenaculum applied to the cervix. He then cut one structure after another, proving that the principal deterrent to prolapse was the paravaginal structures in the upper third of the vagina. These are the same areolar supporting tissues, "the sheets of more or less condensed connective tissue," which the essayist would have us disregard. Furthermore, no discussion of anterior wall reconstruction would be complete without mention of the pubococcygeal fibers of the levator muscle.

The technique as outlined emphasizes the necessity for wide dissection and even distribution of tension but no mention is made of obliteration of dead space. If this principle is followed we again agree in procedure if not in the explanation of the good results achieved. The plication of the fibromuscular sling under the urethra and the pulling in of the lateral supporting structures would thus be accomplished.

RECONSTRUCTION OF THE VAGINA OF DOGS WITH REVERSED SEROMUSCULAR GRAFTS*†

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AMONG the earliest and most provocative attempts at reconstruction of the vagina are the works of Sneguireff[1] in 1892 and Gersuny[2] in 1897, later modified by Schubert.[3] These authors used transplanted segments of the rectum or distal colon to fashion an artificial vagina. Baldwin[4] modified these techniques by using ileum instead of colon, and in the process gained more renown than the aggregate of the previous investigators. These methods, while singularly bold and imaginative, were reported to carry the rather prohibitive mortality of 10 to 30 per cent. Furthermore, the intestinal mucosa often secreted a very irritating and disagreeable discharge.

The earliest use of free skin grafts for reconstruction of the vagina was reported by Heppner[5] in 1872. Graves[6] used full-thickness pedicled flaps from the thigh and labia minora; Frank and Geist[7] applied the tubed pedicle technique of Gillies to this problem with improvement in results. Later Frank[8] proposed a greatly simplified nonoperative technique wherein graded sizes of Pyrex test tubes were pressed into the region of the hymen over an extended period of time. Wharton[9] devised an operation in which a space was made between the rectum and bladder through an incision in the hymenal region; a mold was introduced into this space and maintained in position until epithelization of the space occurred. McIndoe and Banister[10] added to this technique a split-thickness skin graft held in place by the vaginal mold. This was thought to obviate the possibility of incomplete epithelization of the upper end of the newly formed vagina.

A method for the formation of a reversed seromuscular intestinal graft has been previously described and its application in the reconstruction of the urinary bladder[11] and ureters[12] studied. In the present report we have begun to explore the use of this graft for the reconstruction of the vagina.

Method and Material

In this study 10 mongrel dogs weighing from 11 to 15 kilograms were used. In the first group the vagina was excised and reconstructed with the

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previously described graft. In the second group the serosa-lined intestinal grafts were implanted in a cutaneous defect in the anterior abdominal wall in order to observe the histological changes that occur when the grafts are sutured to an epithelial surface. Biopsies of both groups were taken at intervals, fixed in 10 per cent formalin, embedded in paraffin, and stained with hematoxylin and eosin in a routine manner.

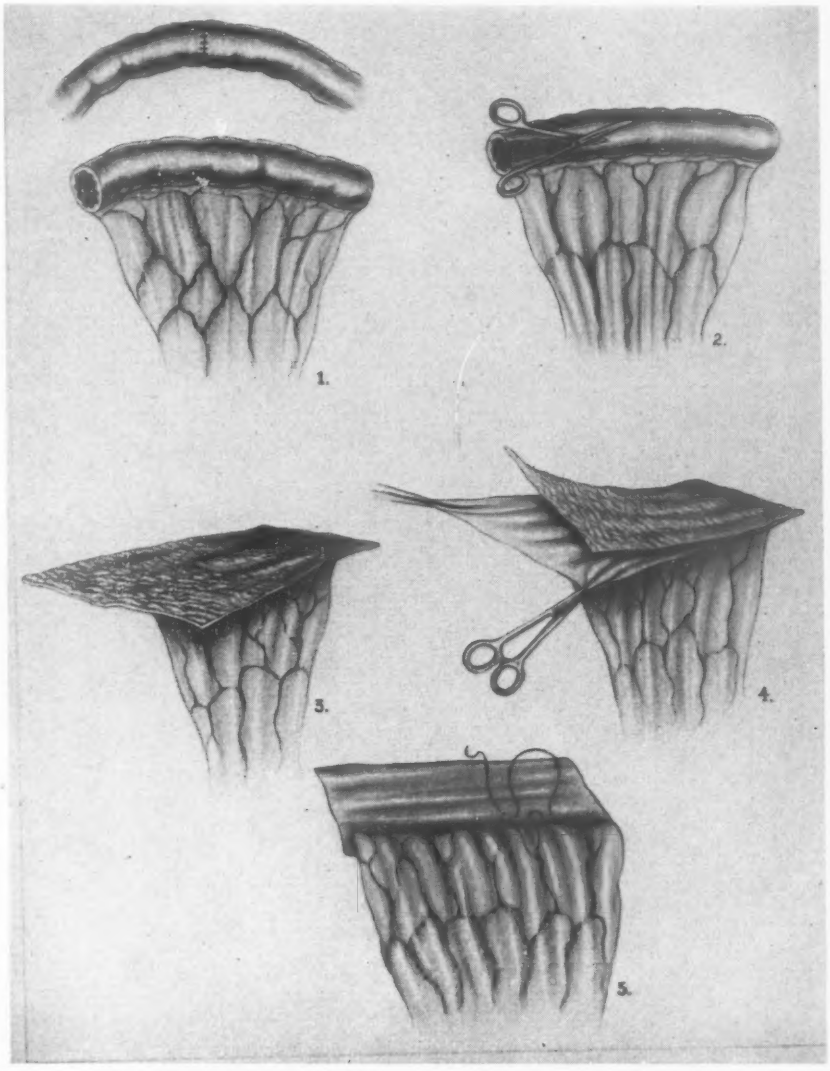

Fig. 1.—*1*, Intestinal segment isolated.
2, Anterior intestinal wall incised.
3, Intestine opened out into a sheet.
4, Mucous membrane removed.
5, Graft turned over or reversed.
(From Shoemaker.[11])

Briefly the technique for reconstruction of the vagina is as follows: The lower abdomen is opened in the midline and a segment of terminal ileum approximately 20 cm. in length is severed from the intestinal tract, and the intestinal continuity restored by an end-to-end anastomosis as shown in the first inset of Fig. 1. The vascular and neural supply of this isolated segment

is maintained through the intact mesenteric pedicle. The isolated segment is then incised longitudinally close to the border of the mesentery and opened out into a sheet. The mucous membrane and submucosa are stripped off, leaving the seromuscular coat with its attached mesenteric pedicle, and the graft is turned over or "reversed" so that the clean, smooth, serosal surface faces the operator (Fig. 1, *5*).

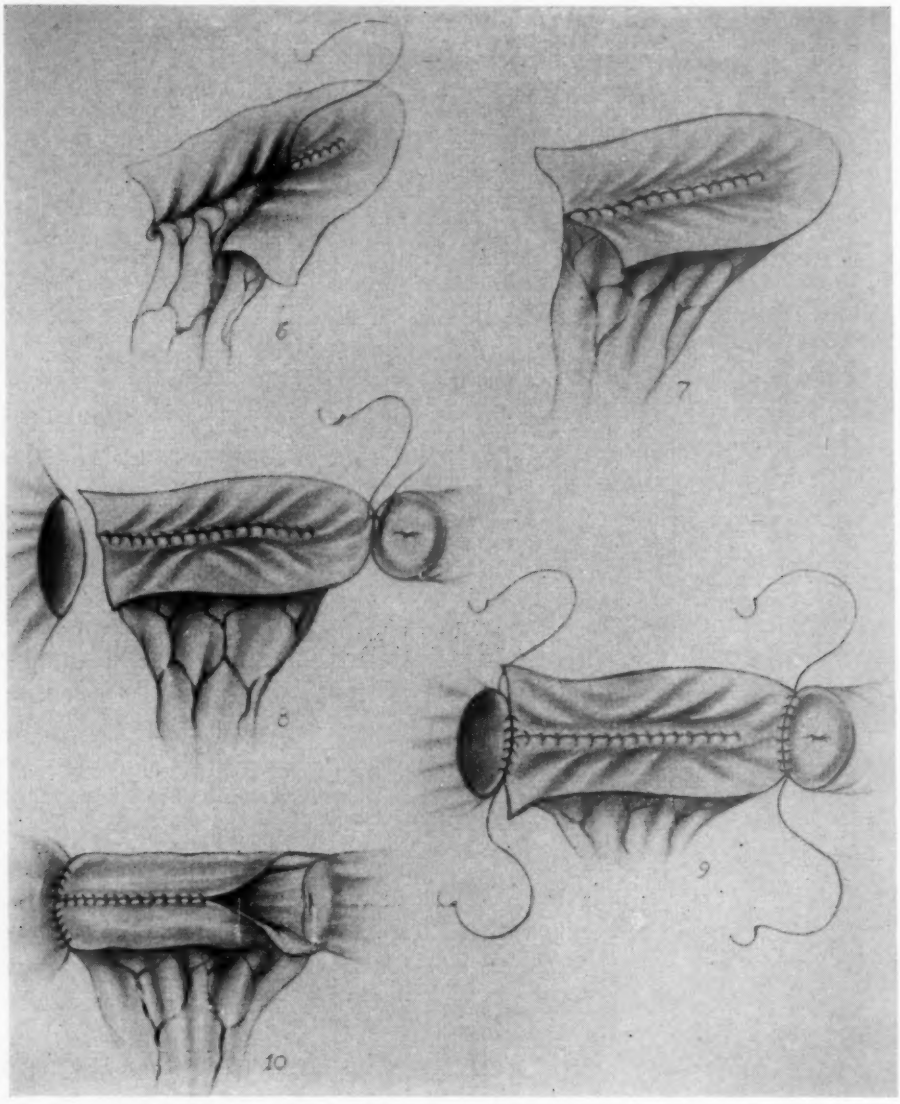

Fig. 2.—*6* and *7*, Graft folded transversely and sutured together excluding the mesentery.
8, Vagina excised; graft attached to cervical stump.
9, Graft sutured to vaginal introitus and cervical stump.
10, Graft closed to form a hollow tube from cervix to outlet.

The long narrow seromuscular graft was then fashioned to form a tubular structure for the substitute vagina. The graft was doubled or folded transversely; the two halves were then sutured to each other close to their mesenteric border, but excluding the mesentery. This formed a trough or "hod" shaped structure. The vagina from the cervix to the urethral orifice was excised.

One end of the trough was sutured to the cervical stump; the opposite end was attached to the cut end of the introitus. The serosal surface of the graft faced inward toward the lumen of the vagina. Continuous sutures of No. 2-0 chromic catgut were brought around anteriorly on both sides of the cervical stump. Similar sutures attached the graft to the circumference of the vaginal introitus. The graft was closed in the midline anteriorly with a continuous suture. Thus, a hollow tube-shaped seromuscular graft, lined with serosa, was substituted for the vagina. The abdominal wall was closed in layers with interrupted cotton sutures (Fig. 2).

A petrolatum gauze was loosely packed into the reconstructed vagina and allowed to remain for 3 to 7 days. No antibiotics or specific therapy was given during the periods of observation.

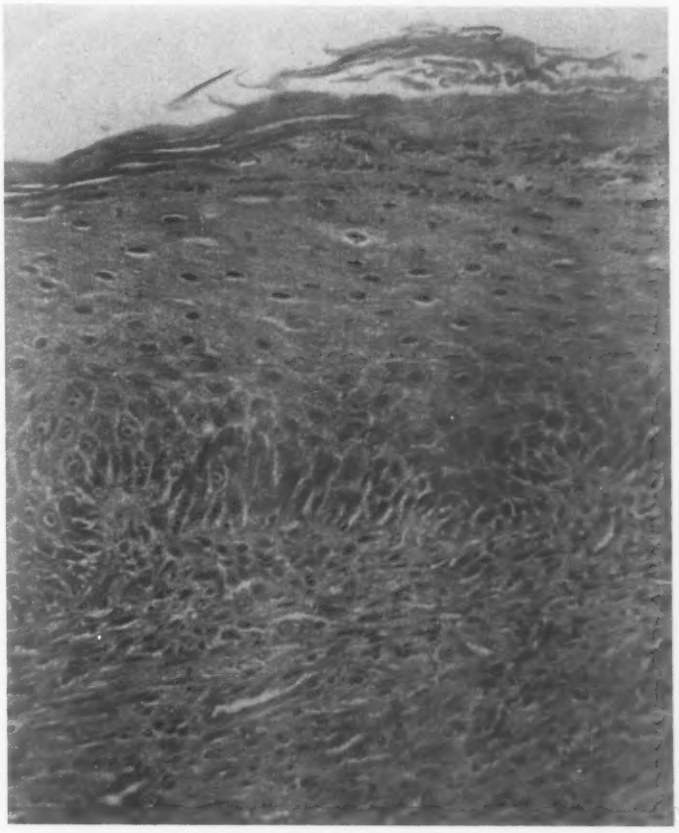

Fig. 3.—Section of the reversed intestinal graft covering a cutaneous defect showing epithelization at 4 weeks after operation. (Hematoxylin and eosin. High power.)

Results

The animals were followed from 2 to 7 months. There were no deaths; healing occurred per primam in all instances. Grossly the graft remained supple and elastic. There was no appreciable shrinkage or loss of length.

In the animals with cutaneous grafts on the exposed anterior abdominal wall, superficial infection and granulation tissue appeared early. Subsequently, this cleared as epithelization progressively covered the area of the graft. Histological studies of biopsies of the intestinal graft sutured into the cutaneous defect showed beginning overgrowth of stratified epithelium at 2 weeks.

At 3 weeks, there was a stratified layer of squamous epithelium with a definite germinal layer and basement membrane. Immediately beneath the epithelium there was a layer of young fibrocytes, capillaries, and inflammatory cells. The muscular layers remained unchanged.

Fig. 4.

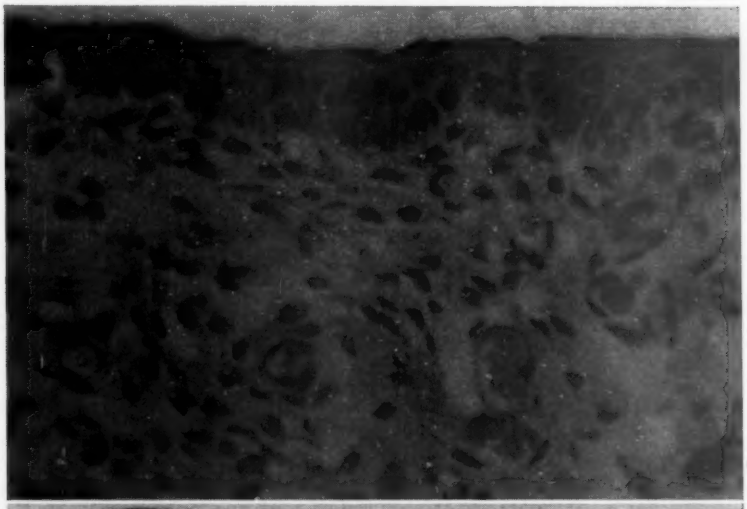

Fig. 5.

Fig. 4.—Beginning epithelization on the surface of the graft 12 days after reconstruction of the vagina. (Hematoxylin and eosin. High power.)

Fig. 5.—Section of the graft at one month showing stratified squamous epithelial lining. (Hematoxylin and eosin. Medium power.)

At 4 weeks, there was a well-defined stratum granulosum and stratum lucidum. Some cornifical squamous cells appeared at the surface. The rete pegs were present although short and thick (Fig. 3).

At 6 weeks epithelization was complete with long, thin rete pegs, germinal layer, stratum granulosum, stratum lucidum, and a well-developed cornified layer. The subepithelial layer was comprised of loose areolar connective tissue, collagen, and capillaries. While the architecture of the muscular layers remained essentially unchanged, beginning disuse atrophy and fibrosis appeared.

Gross observations of the intestinal graft used to reconstruct the vagina revealed less infection and earlier epithelization. At 12 days the graft was covered with columnar epithelium 2 to 4 cell layers in thickness; it was suggestive of the germinal layer of squamous epithelium (Fig. 4). Beneath the epithelial lining there was a well-developed area of fibrous connective tissue and capillaries. The smooth muscle of the intestine was maintained in its original two-layered pattern. At one month the squamous epithelium increased in thickness, and more closely resembled the normal pleuristratified vaginal mucosa (Fig. 5).

Comment

Although previous reported techniques have shown various ways to produce an epithelium-lined cavity in the region of the hymen, it is believed the vaginal reconstruction with reversed seromuscular pedicled grafts is the first attempt to reconstruct this organ with tissue that closely approximates that of the normal anatomy.

In cases of congenital absence of the vagina and psuedohermaphrodism, exploration of the abdomen has been advocated in order to establish definitely the presence and status of the uterus as well as to exclude other associated anomalies. The present study was undertaken with the idea in mind that a definite procedure should be available for the construction of an artificial vagina at the time of the initial exploration. The introduced technique is suggested for the following reasons:

1. The reconstructed vagina becomes lined with stratified squamous epithelium morphologically identical with normal vaginal lining.

2. The graft possesses a smooth-muscle layer similar to that of the normal vagina.

3. The presence of a smooth-muscle layer to maintain strength and tone may be important in preventing fibrosis, shortening, and inelasticity.

4. The reconstructed organ does not undergo contracture or foreshortening.

5. The graft does not secrete mucus or irritating intestinal enzymes, in contrast to the intact intestinal mucosa used in other procedures to form the lining of the reconstructed vagina.

6. The procedure can be performed at the same time the abdomen is explored for evidence of heterosexuality.

Summary

A technique for reconstruction of the vagina with intestinal smooth muscle in the form of a reversed seromuscular graft is described and shown to be a feasible method in the experimental animal.

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PROLONGED LEVARTERENOL BITARTRATE (LEVOPHED*) THERAPY IN SHOCK FOLLOWING REMOVAL OF A LARGE OVARIAN NEOPLASM

Report of a Case

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THE basic and most satisfactory approach to the treatment of shock, especially hypovolemic shock states, consists of blood, plasma, fluid therapy and measures directed to correct the cause of the shock. Not all shock conditions, however, will benefit from blood and fluid therapy. Indeed, in some circumstances, further fluid therapy may not only be valueless but also contraindicated since it may lead to acute heart failure and pulmonary edema. This is particularly true in shock resulting from nonsurgical causes associated with chronic congestive heart failure and myocardial infarction. Even "operative shock" may not respond to fluid replacement and corrective surgery if it has been present for a prolonged period of time.

A large factor in the production of the so-called "irreversible shock state" is irreparable damage to the brain and other vital organs as a result of inadequate perfusion during the state of shock. Therefore, the sooner one returns the blood pressure to a level adequate for the perfusion of the vital organs, the more likely the patient is to recover. When measures aimed at expanding blood volume are not sufficient to overcome the hypotension and shock, adjuvant therapy with vasopressors seems indicated.[4, 5]

A 68-year-old negro woman was admitted to the gynecological service on July 16, 1956, with the chief complaint of abdominal swelling of 10 years' duration. The swelling had recently increased in size and was causing shortness of breath and dyspnea. Physical examination revealed a tremendous, firm, pedunculated, intra-abdominal mass extending from the pubis to the xiphoid. Her blood pressure was 90/60 and pulse 80. Laboratory studies showed the erythrocyte count to be 4 million, hemoglobin 12.5 Gm., blood urea nitrogen 20.1, urea 43.01, urinalysis normal. An electrocardiogram showed T wave inversion in leads V_1, V_2, and V_3, not necessarily indicating myocardial disease. On intravenous pyelogram there was nonvisualization of the left kidney and a large tumor, with calcification, filling most of the pelvis and abdomen.

An exploratory laporotomy was performed on July 18, 1956. Atropine, 0.4 mg., and Demerol, 75 mg., were administered preoperatively. The anesthesia consisted of nitrous oxide and ether. A solid but rather soft tumor, approximately 34 cm. in diameter, was

*Levophed bitartrate, Winthrop Laboratories, New York, N. Y.

noted to arise from the pelvis. The sigmoid was pushed to the right lower quadrant while the cecum and ascending colon were pushed high on the tumor to which they were densely attached. Freeing of the sigmoid entailed entrance into the lumen of this organ. Two separate openings approximately 2 by 5 cm. were made in the ascending colon while it was being freed from the tumor mass. A nodule of the tumor was found to be projecting into the lumen of the bowel. The mass was freed and a bilateral salpingo-oophorectomy and subtotal hysterectomy were accomplished.

Although the patient received 5 pints of blood in continuous infusion during the operation and even though the blood loss was small, the blood pressure dropped to 0/0 immediately after the tumor was removed. Ephedrine, 0.5 c.c. intravenously, brought an immediate but unsustained response in blood pressure. Levophed was administered in the recommended intravenous concentration of 4 μg. per milliliter obtained by addition of a 4 mg. ampule to 1,000 c.c. of 5 per cent glucose in water. There was a prompt rise in blood pressure to 80/60 at a flow rate of 30 drops per minute. In spite of continuous use of blood, the blood pressure could not be maintained at normotensive levels without Levophed. The bowel perforations were closed and a Mikulicz type exteriorization of the sigmoid performed.

Three hours postoperatively the solution containing the Levophed extravasated and the patient went into shock immediately. The drug was then started through an intravenous polyethylene catheter with an immediate rise in blood pressure to 80-100/60. After an additional 3 pints of blood, it became necessary to restrict the volume of intravenous fluids to prevent pulmonary edema. This was done by increasing the concentration of Levophed to 8 mg. per liter of fluid at a slower flow rate. The pressor effect of l-norepinephrine bitartrate* was potentiated with cortisone. The patient was oliguric for the first 24 hours but thereafter the urinary output was normal.

All attempts to discontinue l-norepinephrine resulted in an immediate drop in blood pressure to unobtainable values but there was a prompt resumption of pressor effect on continuation of therapy. Only after 5 days or 118 hours of continuous therapy with l-norepinephrine could it be omitted. The total dosage used over the entire period was 96 mg.

An end-to-end anastomosis was performed on the colostomy on Aug. 15, 1956, and the patient was discharged on the fortieth hospital day. The pathological diagnosis was adenocarcinoma of the ovary and fibromyomas of the uterus. She is living and well one year postoperatively.

Comment

l-Norepinephrine possesses many attributes of an ideal pressor drug because its pattern of selective vasoconstriction is similar to that produced by natural circulatory reflexes, e.g., it favors blood flow to the vital organs at the expense of the less vital skin, etc. l-Norepinephrine was first detected in extracts of organs, such as the spleen, the heart, and the liver, and it was subsequently shown that it was a constantly occurring and specific constituent of adrenergic nerves. This provided the basic support for the theory which has subsequently been verified in several ways, that l-norepinephrine is apparently a natural chemical mediator of sympathetic adrenergic nerve action. It can raise the blood pressure where other potent sympathomimetic drugs, such as Neo-Synephrine, methoxamine, and desoxyephedrine are ineffective.

The vasopressor effect of l-norepinephrine differs from that of epinephrine, in that the predominant action of the former is peripheral vasoconstriction.

*Levarterenol bitartrate U.S.P.

Since epinephrine produces tachycardia, increased cardiac output, and decreased peripheral resistance, there is an elevation of the systolic blood pressure but the diastolic pressure usually remains the same or decreases. Contrariwise, following the administration of l-norepinephrine there is an increase in peripheral resistance without a significant increase in cardiac output. As a result, there is a marked rise in diastolic as well as in systolic blood pressure.[1, 3] This action is more physiological because the heart, like any mechanical pump, can never build up a pressure unless it works against a resistance, in this case the vascular bed. Bradycardia consistently follows the rise in blood pressure, probably due to stimulation of the carotid sinus reflex. l-norepinephrine also causes constriction of the intramuscular vascular bed, whereas epinephrine administered intravenously causes dilatation.[1] The mobilization of blood in shock from the large skeletal muscle mass and its diversion into the central or vital circulation provides a more effective circulation to an area which appears to be crucially involved in "irreversible shock."

This case probably represents a combination of factors leading to peripheral vascular failure. The hemorrhage, anesthesia, and surgical trauma provide only a partial explanation for the hypotension and shock. A major cause, as Eckenhoff[2] has pointed out, appears to be sequestration or pooling of blood in greatly dilated peripheral and splanchnic vessels, with the potential capacity of circulation increasing to a point where "normal" volumes of blood were inadequate to fill the available channels. The enlarged vascular bed has to be filled or the volume of the vascular bed reduced if the patient is to survive.

l-Norepinephrine is not a complete answer to the problem of shock. As Moyer, Skelton, and Mills[4] emphasized, survival of the patient depends primarily on removal of the cause of shock. When l-norepinephrine contributes to resuscitation, it probably does so by mobilizing stagnant blood (peripheral, skeletal, etc.), preventing pooling of blood in these dilated vessels, increasing peripheral resistance, increasing venous return to the heart, and improving blood flow through vital organs by raising blood pressure. [2]

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NEUROFIBROMA FOLLOWING PRESACRAL NEURECTOMY

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PRESACRAL neurectomy as a form of treatment for primary dysmenorrhea has become well established in the practice of gynecology in recent years. It is generally believed, however, that the operation should be done only after a concerted medical program has failed and dilatation and curettage of the uterus has produced no relief of symptoms. Sensory denervation of the uterus usually allows pain-free menses and many of the associated psychic factors clear rapidly.

Technically the operation is not complicated, and the usual operative results are good. Complications after operation may be the same as after any pelvic laparotomy, but occasionally an unusual complication will arise which is worthy of note. The present case is that of a young woman who presented herself with a mass in the operative area about eight months after presacral neurectomy had been performed.

Case Report

A 22-year-old Negro woman of Portuguese extraction was seen in 1955 complaining of severe dysmenorrhea which was not controlled with medication. A dilatation and curettage had been done in 1953 without relief of symptoms. During her menses, pain was incapacitating and physical examination at such times revealed abdominal tenderness and even some rigidity. Pelvic disease which might have contributed to the situation could not be diagnosed, and a presacral neurectomy was felt to be indicated. The operation was performed, as well as appendectomy and uterine suspension, by another surgeon at this hospital. Postoperatively the patient did well with clearing of the symptoms present prior to operation.

She remained asymptomatic for 8 months after operation. At this time abdominal pain was noted which persisted for 2 weeks, and admission was recommended. The patient was menstruating at the time of admission. Physical examination on admission showed a hard, tender midabdominal mass which was fixed to palpation. Pelvic and rectal examinations were negative. Exploratory operation was undertaken. Between the common iliac vessels at the aortic bifurcation was a 5 by 4 cm. mass densely adherent to the vessels and to the sacrum. Clinically sarcoma was suspected, and a biopsy was taken. It was decided to wait for permanent section examination. The biopsy was interpreted as a soft neurofibroma with uniformly myxomatous stroma (Fig. 1). Roentgenograms of the vertebrae were indeterminate for disease. The patient was discharged from the hospital and plans made for readmission and a more definitive resection since a diagnosis of benign neoplasm had been established.

During the following 2 weeks, low back pain became severe and the abdominal mass appeared to increase in size. A barium enema at this time revealed some upward displacement of the colon near the sacrum. On Aug. 23, 1956, a laparotomy was performed, and a 5 by 5 cm. mass found which was peeled from the great vessels with some difficulty. Microscopic examination of the excised specimen was consistent with neurofibroma. Organizing granulation tissue with many foreign-body giant cells of the multinucleated variety was also noted (Fig. 2).

Fig. 1.—Biopsy of tumor mass showing neurofibroma with uniformly myxomatous stroma. (Original magnification ×450.)

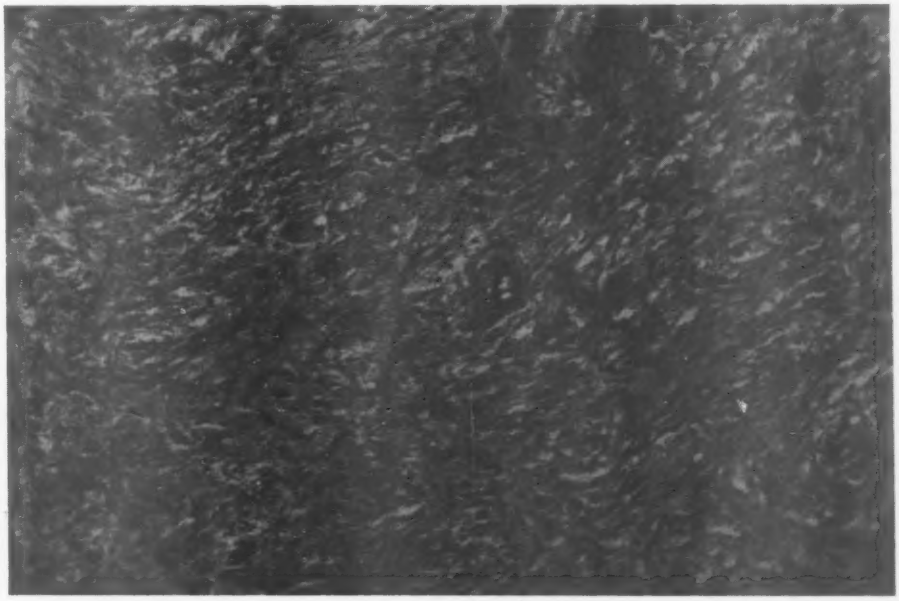

Fig. 2.—Section of the excised tumor showing much organizing granulation tissue. Note the multinucleated foreign-body giant cells. (Original magnification ×250.)

The postoperative course was smooth, save for a minor wound infection. A barium enema 10 days after operation showed some forward displacement of the sigmoid colon. This was interpreted as persistent postoperative inflammation in the area. The patient was discharged 3 weeks after operation, and has had no further abdominal problems to the present time.

Comment

The development of a mass in the operative area after presacral neurectomy is unusual. It is particularly noteworthy because of the symptoms associated with it in the case presented here. The etiology of the tumor is not clear. Evidently a mixed process developed consisting of evolution of a neurofibroma in association with local inflammation from the operative procedure. The former may thus have been the result of the latter. Such a deduction is based on several observations. The neurofibromas seen in von Recklinghausen's disease may be an overgrowth of the sheath of Schwann cells of the nerve involved which simulates neurinomatous growth. Traumatic neuromas may also show such growth.[1] Davis and associates[2] demonstrated that infection at the site of repair of a severed peripheral nerve activates mesodermal proliferation of epineurium and perineurium. It is not unreasonable then to postulate that local infection and postoperative inflammation such as reaction to suture material in the patient here caused such a reaction around the severed ends of the nerve plexus after the presacral neurectomy. Development of the neurofibroma followed. The finding of foreign-body giant cells and organizing granulation tissue further attests to the local inflammatory process that was present. The symptoms cleared after operation and have not returned so that the last operation can be considered to have been specific therapy.

Summary

An interesting case of neurofibroma following presacral neurectomy is presented, with a possible explanation of the development of the tumor.

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TRAUMATIC RUPTURE OF THE APEX OF THE VAGINA TWENTY MONTHS FOLLOWING ABDOMINAL HYSTERECTOMY

A Case Report

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ALTHOUGH rupture of the vagina is not rare, a review of world literature of the decade prior to 1957 disclosed no cases reported following abdominal hysterectomy.

Rupture of the vagina during coitus has been frequently reported.[1, 2, 3, 7] J. Gondim[4] reviewed the continental literature and found over 200 cases reported since 1889, primarily from Italy, France, Spain, and Portugal. Spontaneous vaginorectal rupture following a fall was reported by di Meglio.[5]

Rupture of the vaginal vault following vaginal hysterectomy and associated with evisceration occurring 15 months, 18 months, and 14 years postoperatively has been reported by Dunn,[9] and Fox.[11] Kennedy and Campbell[12] reported 2 cases in which part of the omentum prolapsed into the vagina following vaginal hysterectomy.

In 1951 Beebe and Edwards,[10] in a comprehensive review of lesions of the vaginal vault following complete hysterectomy, reported, "An explanation is lacking for the fact that prolapse of the intestine or oviduct through an opening in the vaginal scar is reported only after vaginal hysterectomy and not after abdominal hysterectomy."

Mrs. W. P., a 39-year-old para x, was admitted to the Plymouth Hospital on April 29, 1957, because of vaginal bleeding following a fall from a 7 foot high shelf while cleaning her home a few hours earlier. During this period she saturated several perineal pads.

Past operative history consisted of a unilateral salpingo-oophorectomy for ectopic pregnancy in 1946 and a total abdominal hysterectomy in 1955, twenty months prior to current admission.

General physical examination showed a well-developed white woman, not obese, who appeared apprehensive and was perspiring somewhat. The pulse was rapid and the blood pressure normal. A suprapubic midline scar was well healed. Vague lower abdominal tenderness on deep palpation was elicited. A small contusion and ecchymosis were present over the left ischial tuberosity. Pelvic examination disclosed no evidence of trauma to the external genitals, perineum, or anus. Bright red blood was slowly trickling from the vagina. A soft lobulated mass was palpable in the posterior vagina. Second-degree cystorectocele was present. On speculum examination, the bleeding was seen to be coming from between lobules of fatty tissue which filled the posterior one third of the vagina. Rectal examination was normal. A catheterized urine specimen was normal.

Repair was carried out under general anesthesia. Exposure was obtained with the usual lateral retractors and weighted speculum and by traction on Allis forceps applied to the lateral angles of the 4 cm. laceration. A continuous No. 3-0 chromic catgut suture closed the peritoneum after replacement of the omentum. The fascia and mucosa were approximated with interrupted figure-of-eight, No. 0 chromic sutures and all bleeding controlled. Since there was no evidence of injury from an intravaginal foreign body, exploratory laparotomy was not carried out.

The postoperative course was afebrile and uncomplicated. Penicillin, 400,000 units, and streptomycin, 0.5 Gm., were given intramuscularly every 8 hours for 3 days. Triple Sulfa Cream was instilled twice daily. The patient was discharged on the third postoperative day with instructions to rest for one week and return to the clinic. When she was last seen on Dec. 11, 1957, the apex of the vagina was well healed and well supported.

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Obstetrics

THE PERMEABILITY OF THE RABBIT PLACENTA TO HOMOLOGOUS ALBUMIN

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NUMEROUS data have been accumulated concerning placental protein passage and an attempt is made in this report to review this work and to add some original observations on the placental transfer of homologous albumin in the rabbit.

As early as 1913 Morel[1] reported no difference in amino acid concentrations in fetal and maternal circulations. As more refined means of quantitating amino acids were evolved, fetal amino acid levels have been found to be from one to five times the levels in the mother. Dietary proteins tagged with C^{14}, when given to pregnant dogs, were found in considerable quantity in the fetus in a relatively short space of time.[2-7] This is an example of an active process being carried out by the placenta for certain substances. This active transfer process may well explain the actual reduction of plasma proteins in the mother during pregnancy. Clemetson,[5] in England, stated that the placental transfer of amino acids to the fetus is impaired in toxemia. Page[6] has studied the transfer of histidine and indicates the high degree of selectivity exercised by the human placenta. He observed the transfer of naturally occurring L-histidine and the unnatural isomer D-histidine. The L-histidine was able to pass the placenta very rapidly while the D-histidine took hours to pass.

The placental transfer of protein has been most widely studied by the serologists. Numerous investigators have demonstrated that antibodies cross the human placenta readily. Among those so proved have been antibodies against toxoplasmosis, tetanus, typhoid, diphtheria, measles, smallpox, polio, mumps, equine encephalitis, isoagglutinins determining blood groups, protein-sensitizing antibodies, complement-fixing antibodies, bacteriolysins, hemolysins,

and precipitins.[8-21] These observations hold true for the human, rabbit, and rodent placenta. They do not follow in the dog, goat, horse, sheep, or pig. In the first-mentioned group there is a placental partition of only one cell layer while in the other group a multiple-layered partition is present, thus serving as a barrier to the passage of antibodies.

Osborn and his group[16] demonstrated an increasing permeability of the human placenta to diphtheria antibodies as the period of gestation lengthened. They found extremely low titers in infants weighing under 1,200 grams.

Concerning polio, antibodies were found to pass to the fetus from mothers immunized with Salk vaccine. There was, however, no correlation of fetal and maternal antibody titers. The antibodies acted as exogenous gamma globulin in that they were excreted at a rate which gave them a half life of 50 days.[22]

Recently, the transmission of fetal hemoglobin across to the maternal circulation has been demonstrated. The fetal hemoglobin in the mother's blood varied usually from 0 to 2.2 per cent. In approximately 5 per cent of these cases, however, fetal hemoglobin was present in significant concentrations. In this latter group of cases there was apparent correlation with a hemolytic process in the fetus. Other reports show a correlation in the appearance of fetal hemoglobin in the maternal circulation with the degree of anemia of some newborn infants. They postulate an actual fetal hemorrhage into the maternal circulation.[23-27]

Whipple,[28] in Rochester, New York, using homologous "tagged" dog and rabbit plasma observed that dog plasma does not pass across the placenta. The rabbit plasma was transferred slowly, however.

A review of the literature on placental transfer reveals little experimental data related specifically to the transfer of the albumin fraction of the serum proteins. It is readily accepted, and has been duly demonstrated, that the gamma globulin fraction of the serum proteins crosses the placenta.[10, 13, 16, 17, 21] It has also been established that the amino acids used in protein synthesis easily cross the placenta.[2-5, 7, 8] In view of the fact that the molecular size of albumin is smaller than that of globulin, it was felt that albumin should cross the placental barrier.

It was with these thoughts in mind that we undertook the current investigations.

Materials

Albino rabbits averaging about 10 pounds and in the last week of gestation were obtained. Prior to this a rabbit had been bled and, in the laboratory of Dr. Ernst Witebsky at the Medical School of the University of Buffalo, by means of ultracentrifugation, the albumin fraction of the serum protein was separated. Electrophoretic analysis of this preparation revealed that it contained over 80 per cent albumin with the rest being protein globulins. The rabbit albumin was then labeled with iodine^{131} in similar fashion to the method used with human serum albumin (RISA*). The solution contained 2 mg. of albumin per cubic centimeter. All iodinated albumin fractions were

*Abbott Laboratories, North Chicago, Ill.

dialyzed prior to injection into the animals. The original dialyzed preparation contained only 3 per cent free iodides and had an activity of 0.23 mc. per cubic centimeter.

Method

An average dose of 0.15 mc. of the radioactive rabbit albumin was injected into the ear vein of the pregnant rabbit. After a definite time interval (1, 6, 15, and 24 hours) the rabbits were anesthetized with Pentothal sodium and cesarean section was performed. Each fetus in the litter was washed, dried, weighed, and decapitated. Blood was collected from the great veins of the neck. At the same time a specimen of blood was taken from the maternal vena cava. Oxylate was used as an anticoagulant. The fetal blood specimens were pooled and both they and the maternal specimens were centrifuged and a measured amount of the plasma was counted in a deep-well scintillation counter. Following this, 0.01 ml. of both maternal and fetal plasma was subjected to electrophoresis. A Spinco Paper Electrophoresis Cell, Durrum type, with a barbiturate buffer, was used. The radioactivity of the separated plasma proteins was then counted in the deep-well scintillation counter. An additional refinement of dialysis was used in the latter experimental animals to separate the plasma proteins from any free iodides present. The results of dialysis and electrophoresis were compared.

Results

The figures for Series No. 1 illustrated the results obtained following one hour after the radioactive albumin was given to the maternal rabbits. As can be seen, the percentage of activity of fetal plasma to maternal plasma is negligible.

Series No. 1. Rabbits One Hour Post Injection

NO.	MATERNAL (C/M/C.C.*)	FETAL (C/M/C.C.*)	%
1	6,400	156	0.3
2	31,744	512	1.6
3	70,144	1,026	1.4
4	41,470	819	1.9
5	51,700	768	1.5

*Counts per minute per cubic centimeter in maternal and fetal plasma.

Series No. 2. Rabbits 6 Hours Post Injection

NO.	MATERNAL (C/M/C.C.)	FETAL (C/M/C.C.)	%
1	38,400	256	0.7
2	14,500	128	0.9

Series No. 3. Rabbits 16 Hours Post Injection

NO.	TOTAL ACTIVITY MATERNAL PLASMA (C/M/C.C.)	TOTAL ACTIVITY FETAL PLASMA (C/M/C.C.)	% TOTAL ACTIVITY F/M PLASMA	MATERNAL PROTEIN (C/M/C.C.*)	FETAL PROTEIN (C/M/C.C.*)	% ACTIVITY F/M PROTEIN
1	53,760	25,600	47.6	40,700	2,600	6.4
2	99,840	46,000	46.1	72,700	2,600	3.6
3	58,880	48,640	82.6	49,900	1,600	3.2

*These values represent the concentration of radioactive protein, principally albumin, following separation by electrophoresis of any free radioactive iodine.

SERIES NO. 4. RABBITS 24 HOURS POST INJECTION

NO.	TOTAL ACTIVITY MATERNAL PLASMA (C/M/C.C.)	TOTAL ACTIVITY FETAL PLASMA (C/M/C.C.)	% TOTAL ACTIVITY F/M PLASMA	MATERNAL PROTEIN (C/M/C.C.*)	FETAL PROTEIN (C/M/C.C.*)	% ACTIVITY F/M PROTEIN
1	64,000	30,720	48.0	34,000*	1,000*	3.0
2	58,880	7,680	13.0	32,180*	1,600*	5.0
3	61,440	15,360	25.0	42,200*	1,600*	4.0
4	39,680	28,710	72.4	29,800*	2,800*	9.4
			Dialysis:	30,400	1,290	4.2
5	19,520	3,440	17.0	16,000*	2,200*	13.8
			Dialysis:	20,780	1,420	6.8

*These values represent the concentration of radioactive protein, principally albumin, following separation by electrophoresis of any free radioactive iodine.

Comment

Reference to Series Nos. 1 and 2 shows a minimal activity present in fetal plasma up to 6 hours following administration of the radioactive albumin preparation. Because the radioactivity of the fetal plasma was of such negligible amounts, it was felt not necessary to identify the location of the activity either by electrophoresis or dialysis.

In Series Nos. 3 and 4, the rabbits were sacrificed 16 and 24 hours following injection of radioactive albumin. The results obtained in these series are somewhat different from those of the earlier studies. The total amounts of radioactivity in the fetal plasma reached considerable proportions, however inconsistently, ranging from 13 to 72 per cent of the comparable total activity in the maternal plasma.

It is known that there is a continuous breakage of the iodine-albumin bondage and that any free iodine will readily cross the placental barrier in concentrated amounts. The portions of activity in the fetal and maternal plasma which were due to protein-bound iodine and free iodine were then determined. Electrophoresis and dialysis were used to accomplish this.

Following separation of the free iodine from the plasma protein, there was a marked reduction in the total activity in the fetal plasma but only a slight reduction in the total activity in the maternal plasma. From this it was assumed that the major portion of activity in the fetal plasma was due to free iodine and that only a small portion was due to iodine-bound albumin. It is conceivable that not all of this iodine-bound albumin was transferred across the placenta. Some of this radioactive albumin may be due to free iodine which was incorporated into fetal thyroxine which would circulate bound to albumin in the fetus.

Dialysis was performed on the plasma of the last 2 animals in the 24 hour series. The figures obtained were both lower than those by electrophoresis and were probably of more significance.

In conclusion, it can be said that although albumin appears to cross the placenta, the rate of transfer is extremely slow for 24 hours. This supports the hypothesis that fetal protein nutrition is dependent on simple amino acid transfer rather than passage of the larger protein fractions.

Summary

Experimental work has been presented on the placental passage of albumin with the use of radioactive iodinated rabbit albumin in term pregnant rabbits.

We are indebted to Dr. E. Witebsky, Dr. S. Shulman, and their laboratory staff for their help. We also wish to thank Dr. D. W. Stiff and Mr. Ted. Bow of the Radio-isotope Laboratory of the E. J. Meyer Memorial Hospital for their assistance and use of their facilities, and Miss R. Palmer of the Clinical Laboratory for performing the electrophoresis.

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THE TRANSMISSION OF TRANSFUSED SICKLE-TRAIT CELLS FROM MOTHER TO FETUS

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IN 1940 Landsteiner and Wiener[1] made their first report on the Rh factor and established that the antigen was located on human erythrocytes.[2] This was followed by the recognition of its role in erythroblastosis fetalis by Levine and his associates[3] in 1941. In order to explain isoimmunization the old concept of the separate integrity of the fetal and maternal circulations was subjected to critical reappraisal.

Several investigators approached this problem by devising experiments to show the transmission of maternal erythrocytes across the placental barrier. In 1946 Hedenstedt and Naeslund[4] injected elliptocytic blood into 2 pregnant women. They demonstrated the elliptocytes in the blood of one of the infants and noted that the placenta in this case had many sites of bleeding and infarction. Naeslund and Nylin[5] injected erythrocytes tagged with radioactive phosphorus (P^{32}) into 6 pregnant women prior to delivery. In one of the cases, they were able to demonstrate a significant degree of radioactivity in the infant's erythrocytes. In 1951 Naeslund[6] transfused erythrocytes which had been tagged with radioactive iron (Fe^{59}) into 7 pregnant women. His findings in the blood of the infants of 4 of these women suggested that the radioactive red blood cells had crossed the placenta. In 1955 Mengert and his associates[7] employed erythrocytes tagged with Fe^{59} and performed 29 experiments. Significant amounts of radioactivity were demonstrated in the fetal red blood cells in 25 of the experiments. The investigators considered the method with Fe^{59} cumbersome and vulnerable to error. They did 2 additional experiments utilizing donor blood with the sickle-cell trait. This blood was injected into 2 pregnant women. Sickle cells were demonstrated in the blood of both infants, indicating that the sickle-trait cells had crossed the placenta.

Material and Methods

The purpose of this investigation was to determine by yet another method whether intact maternal erythrocytes cross the placental barrier. Donor blood with the sickle-cell trait but without sickle-cell anemia was selected for this purpose. When erythrocytes with the sickle trait are exposed to a decreased oxygen tension, they assume a characteristic sickled configuration

which is easily recognized. A group of pregnant women was therefore injected with sickle-trait blood and the blood of their infants was examined for sickle cells.

Blood donated to the Kings County Hospital Blood Bank was examined for the sickle trait. A 1 per cent isotonic solution of sodium bisulfite in distilled water was prepared and a large drop of the solution was mixed with a small drop of blood on a slide. A coverslip glass was immediately applied with gentle pressure to prevent floating, and the excess solution-blood mixture at the edges of the preparation was blotted. Care was taken to insure the freshness of the solution, since it deteriorates rapidly at room temperature. With this method, sickling occurs promptly and is usually complete within 30 minutes to 1 hour. The Blood Bank donor requirements excluded individuals with sickle-cell anemia. Therefore, it was assumed that all donor bloods in which sickling was demonstrated came from individuals with the sickle-cell trait.

The subjects of this study were 25 Rh-positive pregnant women at or near term. Specimens of their blood were examined for sickle cells and in all except one none were found. When available, the husband's blood was also examined for sickling. The selection of subjects in this study was governed largely by the blood group of the sickle-trait donor blood that was available. They ranged in age from 17 to 38 years. The distribution included 18 Negroes, 4 Puerto Ricans, and 3 whites.

Twenty-one of the subjects were transfused with 500 ml. each of sickle-trait whole blood preserved in A.C.D. solution. In 3 instances (Cases 1, 2, 3), the supernatant plasma in 500 ml. of whole blood was removed, allowing the sickle-trait cells to be given in a reduced volume. The elapsed time, between the end of the transfusion and delivery, ranged from 40 minutes to 153 hours and 2 minutes. Nineteen of the women were delivered vaginally and 6 by cesarean section.

Whole blood was collected both from the umbilical cord at delivery and from the mother within 12 hours after delivery. A combination of dried ammonium and potassium oxalates was used as the anticoagulant. The blood from the umbilical cord was collected with the utmost care to prevent contamination with maternal blood.

Sickle-cell preparations of the mother's and infant's bloods were prepared by the method described above. In order to prevent drying, the preparations were covered with Petri dishes to which moist filter papers had been attached. They were examined for sickling at intervals of 15 minutes, 30 minutes, and 1 hour. When sickle cells were present, the sickling process occurred earlier and was more complete among the red blood cells near the edges of the preparation. A crude estimate of the number of sickle cells was made by counting the number of sickle cells in 2,000 consecutive red blood cells near the edges of the coverslip glass. When sickle cells were found in the blood from an umbilical cord, the infant's blood was, when possible, examined 8 weeks later in order to rule out the possibility of an inherited sickle trait.

Results

The results of this study are listed in Table I. Sickle cells were found in the umbilical cord blood of the newborn infant in 3 of the 25 cases studied. Case 2 was an 18-year-old primigravida who was delivered vaginally with the aid of forceps. Case 6 was a 21-year-old multipara who had an uneventful vaginal delivery. Case 13, a 19-year-old primigravida, was delivered by cesarean section because of a breech presentation and prolonged rupture of

TABLE I. DATA ON 25 CASES STUDIED

CASE NO.	AGE	RACE AND NATIONALITY	SICKLE-CELL PREPARATION	GRAVIDITY	PARITY	DELIVERY	TIME FROM TRANSFUSION TO DELIVERY		% SICKLE CELLS POST PARTUM		
							HOURS	MINUTES	MOTHER	INFANT BIRTH	INFANT 8 WKS.
1	21	N	Neg.	iii	ii	Vaginal	1	53	11.5	0	—
2	18	W	Neg.	i	0	Vaginal	10	21	12.1	2.6	0
3	26	N	Neg.	iii	ii	Vaginal	0	40	13.7	0	—
4	18	N	Neg.	i	0	Vaginal	7	19	13.0	0	—
5	17	N	Neg.	i	0	Vaginal	7	52	13.5	0	—
6	21	P.R.	Neg.	iii	ii	Vaginal	21	0	12.4	0.2	0
7	28	W	Neg.	ii	i	Vaginal	1	12	10.3	0	—
8	34	N	Neg.	iv	iii	Cesarean section	5	10	11.9	0	—
9	22	N	Neg.	i	0	Vaginal	26	40	10.6	0	—
10	21	N	Neg.	ii	i	Cesarean section	13	0	12.1	0	—
11	34	N	Neg.	xi	x	Vaginal	1	30	13.4	0	—
12	35	P.R.	Neg.	iii	ii	Cesarean section	79	30	9.6	0	—
13	19	P.R.	Neg.	i	0	Cesarean section	0	47	11.9	2.3	—
14	33	N	Neg.	xii	ix	Vaginal	34	20	12.1	0	—
15	36	N	Pos.	viii	vii	Vaginal	—	—	—	0	—
16	17	N	Neg.	i	0	Cesarean section	39	30	10.8	0	—
17	22	N	Neg.	v	iv	Vaginal	2	56	12.2	0	—
18	18	W	Neg.	i	0	Vaginal	1	54	13.5	0	—
19	22	P.R.	Neg.	iv	iii	Vaginal	153	02	11.3	0	—
20	23	N	Neg.	i	0	Vaginal	32	10	13.0	0	—
21	20	N	Neg.	i	0	Vaginal	2	50	12.3	0	—
22	25	N	Neg.	ii	i	Vaginal	8	29	14.3	0	—
23	17	N	Neg.	i	0	Vaginal	2	55	12.1	0	—
24	38	N	Neg.	iii	ii	Cesarean section	15	30	12.7	0	—
25	26	N	Neg.	ii	i	Vaginal	5	13	13.3	0	—

the membranes without labor. The placenta in each of the 3 cases was normal on gross inspection. The blood of the infants in Cases 2 and 6 was examined for sickle cells when they were 8 weeks old. None were found, indicating that the sickle cells demonstrated in the umbilical cord blood had crossed the placenta and were not the result of an inherited sickle trait. A similar follow-up study of the infant in Case 13 could not be done. This infant had contracted a parenteral diarrhea and died at the age of 5½ weeks. Sickle cells, when present, can be identified in histologic tissue sections. None were found when the sections of the infant's organs were examined.

Case 15 presented an interesting natural experiment. This woman had the sickle-cell trait. She was included in the study because there was a possibility that her infant would not inherit the sickling trait. Two of the variables present in all of the other cases, the amount of sickle-trait blood injected ante partum and the elapsed time from the end of the transfusion to delivery, were not factors in this case. All of her erythrocytes had the ability to sickle. Nevertheless, no sickle cells could be demonstrated in the infant's blood.

Comment

The placental passage of sickle-trait cells in 3 of 25 experimental subjects adds to the already existing evidence that in a small percentage of patients maternal red cells traverse the placental barrier and are found in appreciable numbers in the fetal circulation. The mechanism of transfer is obscure. While breaks are known to occur in the fetal circulation,[8-10] the pressure relationships are thought to be such that direct passage must always occur from fetus to mother. The infant arterial pressure at birth is 60-70 mm. of mercury while the venous pressure in the umbilical cord is 30-40 mm. of mercury. This would make the capillary pressure in the villi about 45 mm. of mercury.[11] The pressure of maternal blood in the intervillous space with the uterus at rest is about 10 mm. of mercury.[12] While this pressure rises markedly with uterine contractions, a proportionate rise in fetal pressure must also occur.

Unless the known data on infants are not valid for the fetus in utero, direct transfer of maternal cells against the pressure gradient is not feasible. Furthermore, although nothing is known about the pressure relationships of the human fetus in utero, the venous pressure cannot fall below the amniotic fluid pressure which for all intents and purposes is the same as the intervillous space pressure.

The only remaining possibility is active transfer by the process of planocytosis which has been shown to occur for particulate matter.[13]

Making certain rough assumptions from the data in Table I, in at least one instance* the fetus must have received at least 5 ml. of sickle-trait cells. Should the placenta be unable to distinguish between sickle-trait and normal maternal cells, the transfusion to accomplish this must have been a bit more than 40 ml., which is altogether unlikely. One is left with the rather fantastic assumption that the microvilli distinguish between natural and unnatural maternal cells, engulfing only the latter.

*Case 2, fetal red-cell mass estimated at 200 ml.

The facts of transfer can no longer be denied. The mechanism remains a baffling mystery.

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FREE AMINO ACIDS IN HUMAN AMNIOTIC FLUID, FETAL AND MATERNAL SERUM

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THIS paper deals with the qualitative and quantitative evaluation of the free amino acids present in normal human maternal blood serum, fetal blood serum, and amniotic fluid at the time of parturition. Values for free amino acid nitrogen in maternal and cord blood, in both normal and toxic cases of pregnancy, have been determined by many investigators using the Van Slyke[1] and the Van Slyke-Hamilton[2] methods. These studies recorded the total amount of free amino acid nitrogen in all the amino acids of the serums being investigated, but they only gave the amino acid nitrogen total and not the quantitative distribution of each amino acid constituent. There have also been some investigators who combined the Van Slyke-Hamilton method with paper chromatographic methods which used arbitrary standards; hence, their results were nonquantitative. None of the foregoing studies included a quantitative study of the free amino acids in the amniotic fluid.

The importance of free amino acids is the contribution they make to growth. They are essential for the synthesis of proteins and enzymes. Defined, they are ammonia-substituted organic acids which may be linked together by peptide bonds to form proteins. Consequently, the detection of their presence, concentration, and distribution in any living matter, together with qualitative identification, is of vital informative value. Therefore, the importance of both quantitative and qualitative analysis by chromatographic methods of such free amino acids as may be found present in the three extracellular fluids of the human gestation period at term is evident.

A survey of important contributions to this field shows that as early as 1913, Morel and Mouriquand,[3] using the 1912 Van Slyke[1] method of amino acid estimation, found no differences between human fetal and maternal whole blood amino acid concentrations, and therefore they appeared to be justified in the assumption that there is a simple diffusion of amino acids across the placenta. In contradistinction, Rabinovitch[4] in the following year, employing the same method, obtained other results: the fetal levels exceeded the maternal. In 1917, Morse[5] applied the Van Slyke method for the determination of free amino acid nitrogen of the blood in cases of normal and complicated pregnancy and also in the newborn infant, and stated "that though the difference between the concentration of amino acids in the two circulations is small, it is in favor of the fetus in 70 per cent of the cases, and the higher level in that organism prevents the acceptance of simple diffusion as the explanation of the placental

exchange. . . . In other words, the requirements of the fetus cause no increase of the substances in the maternal blood out of which protein is constructed." He assumed that the passage of amino acids from maternal and fetal blood through the placenta had the property of absorption in order to "protect the fetus against loss of material intended for the construction of protein." In 1947, Bonsnes[6] reported the "reduction [of free amino acids] in plasma in human pregnancy, and these low values were maintained throughout labor and until parturition." He concluded that "the diminution probably results from the avid removal of amino acids by the placenta."

The development by Hamilton and Van Slyke[2] in 1943 of an improved analytical method for the determination of amino acid nitrogen opened the way to further investigation. In 1948, Christensen and Streicher[7] observed in two instances growth acceleration associated with elevation of the cellular concentrations of amino acids. Using the Van Slyke-Hamilton method,[2] they did a comparison study of certain amino acid concentrations in fetal and maternal plasma and tissues. They found "the concentration of both glycine and the non-glycine, non-glutamine ('residual') alpha-amino nitrogen of skeletal muscle about 3 times as high in the fetus as in the maternal guinea pig," and reported "similar observations" in ". . . the rabbit." They stated, "Higher fetal concentrations may be attributed to two factors: (1) concentration of amino acids by the placenta; and (2) greater concentrating activity of fetal muscle than of maternal muscle." "In human fetal plasma, amino acids were observed to be 1.5 to 2 times as concentrated as in the maternal plasma." Fetal-maternal ratios were: 5/1 for the guinea pig, 1.5 to 2/1 for the rabbit, and 1.7 to 1.8/1 in the human. Their experiments revealed active placental transfer of amino acids by showing how glycine feeding to pregnant guinea pigs produced a higher concentration of this substance in the fetal than in the maternal plasma. "Feeding L-glutamic acid resulted in concentrations of over 40 mg. per cent of alpha-amino nitrogen in the fetal plasma, without any effect upon the glycine distribution." During pregnancy, the amino acid concentrations of plasma were decreased in both human and guinea pig subjects.

In 1950, Crumpler, Dent, and Lindan[8] presented some conclusions on the "Amino Acid Pattern in Human Foetal and Maternal Plasma at Delivery." They found in nearly every case a higher concentration of alpha-amino nitrogen in the fetal plasma than in the maternal. "The increase involved all the amino acids commonly found in these fluids." They suggested that "the placenta acts as an amino acid pump assisting the fetus to synthesize proteins." The 4 out of 9 cases in which a low fetal/maternal ratio for the plasma alpha-amino nitrogen occurred were those in which the mother had definite toxemia of pregnancy, suggesting impairment of placental function as a feature of toxemia. This investigation confined its study of the amino acid content to the fetal and maternal blood plasma only; it did not investigate the amniotic fluid. It employed both chemical and chromatographic methods, though the latter was not quantitative in method; and therefore, being arbitrary, it did not give the amounts and distribution of the specific amino acids present.

Employing maternal blood only, Burt,[9] in his investigations of " 'Combined' and Free Plasma Alpha-Amino Nitrogen in Normal Pregnancy and Toxemia" confirmed and extended the results reported by Bonsnes. Total alpha-amino nitrogen of plasma decreased in pregnancy, rising to normal levels 24 to 72 hours post partum. Variations present in the data of other authors were noted (such as decrease in free alpha-amino nitrogen concentration of plasma in pregnancy), but Burt reported "Serial determinations made on normal pregnant women and on patients with toxemia of pregnancy showed no apparent differences in plasma levels of alpha-amino nitrogen." He found " 'Combined' alpha-amino nitrogen of plasma unaltered by pregnancy or toxemia of pregnancy."

Clemetson and Churchman[10] compared 43 pairs of maternal and fetal plasma samples and "in every case found the fetal amino acid level higher than the maternal." They noted exceptional results in cases of umbilical "cord round the neck"—a ratio decrease of 1.38/1. In this cord obstruction ratio, they found "strong evidence that the lowering of the maternal amino acid level in pregnancy is due to the transfer of amino acids to the fetus."

This study presents the quantitative chromatographic comparison of the free amino acids found in human amniotic fluid, fetal blood, and maternal blood drawn at the time of parturition.

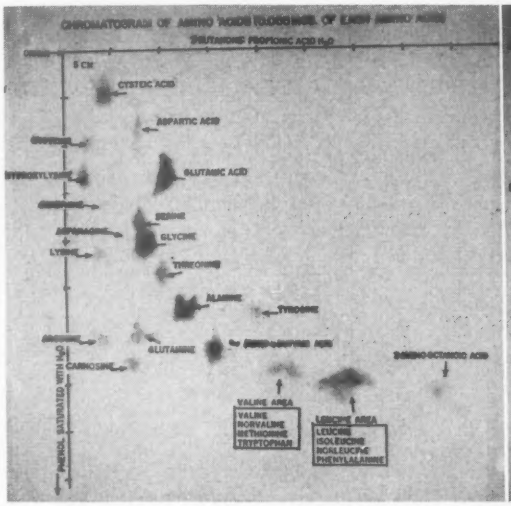

Fig. 1.

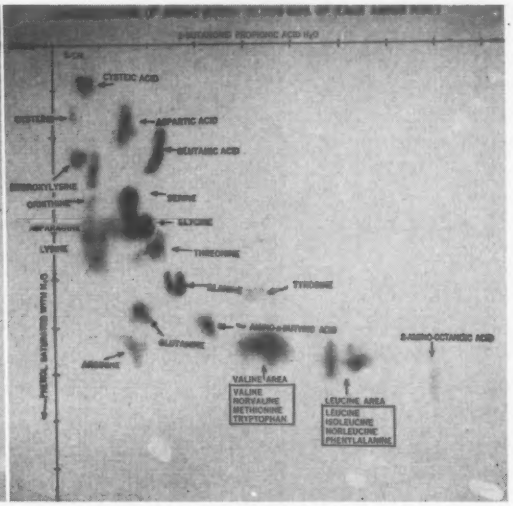

Fig. 2.

Chromatographic Method

In order to precipitate the proteins present in amniotic fluid, maternal serum, and fetal serum, acetone is added to them in a proportion of 600 lambda of acetone to 200 lambda of the respective fluid. The acetone supernatant is spotted on a 6 by 22.5 inch sheet of Whatman No. 3 chromatography paper. This paper is run for 7 hours with a solvent system composed of 2-butanone (75 ml.), propionic acid (25 ml.), and glass-distilled water (30 ml.). The long edge of this sheet is then sewn to an 18.25 by 22.5 inch sheet of Whatman No. 3 chromatography paper. The sheet is turned 90 degrees and run for 20 hours in a second dimension, employing glass-distilled phenol saturated with glass-distilled water as solvent. The amino acid areas are developed by spraying with ninhydrin and are identified by comparison with previously prepared, quantitatively determined maps of the distribution of 32 known amino acids (Figs. 1 and 2). Separation of the 4 amino acids within the "valine area" and "leucine area" may be accomplished by sewing these areas to additional strips of paper and rechromatographing with other solvents.*

Results

A. Invariables.—

1. In every one of the 7 cases examined, the total free amino acid content of the amniotic fluid (Fig. 3) at the time of parturition is less than that of the maternal serum (Fig. 4) at the time of parturition.

*The details of the chromatography procedure will be published elsewhere.

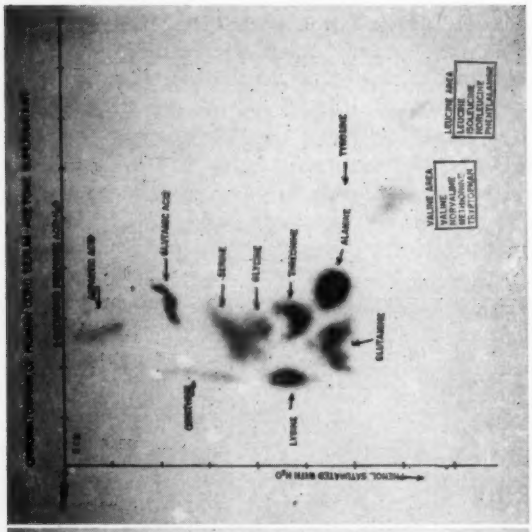

Fig. 5.

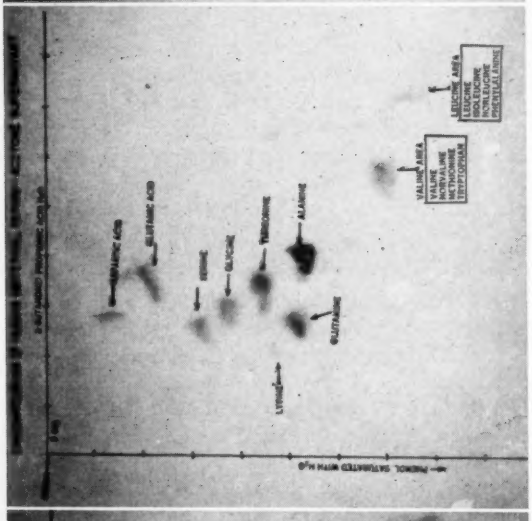

Fig. 4.

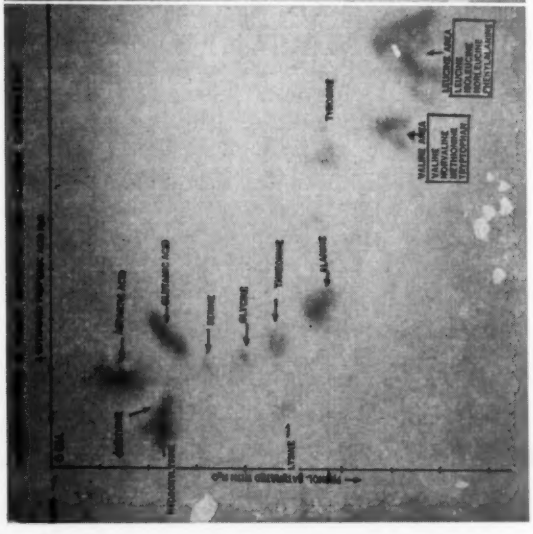

Fig. 3.

2. In every one of the 7 cases examined, the total free amino acid content of the maternal serum at the time of parturition is less than that of the fetal serum (Fig. 5) at time of parturition.

B. Variables.—Considered specifically or individually, the free amino acids show remarkable variability. For example we find these constants: glutamic, serine, glycine, threonine, alanine, lysine, the valine area, the leucine area, always detectable in both the amniotic fluid and the sera.

But the following free amino acids appear irregularly: hydroxylysine (3 times), cysteic (5 times), carnosine (5 times), arginine (12 times), ornithine (13 times), glutamine (16 times), tyrosine (17 times), and aspartic (20 times) (Table I).

The absence of an amino acid may perhaps be due to the detectability limit of the individual amino acid because of the small amount of material used in these experiments. Thus the method employed requires the presence of more than one gamma (0.001 mg.). If more than 200 lambda are used, the separation of the amino acids is more difficult to obtain and consequently the identification. Furthermore, there is marked variability in the concentration of all. There is no quantitative pattern apparent, no proportional increase in the concentration of these specific free amino acids.

Comment

The findings reported here for human amniotic fluid and maternal serum differ greatly from those previously reported on rat amniotic fluid and maternal serum.[11] Whereas human amniotic fluid showed a lower concentration of specific free amino acids than human maternal blood serum, in contrast, a higher concentration of specific free amino acids occurred in rat amniotic fluid than in rat maternal serum.

The study of free amino acids in rat amniotic fluid and maternal serum showed an increase in the concentration of these amino acids throughout the gestation period. But it was also noted that they did not vary proportionally one to another but exhibited individual patterns of concentration throughout the gestation period. Since the rat gestation process revealed this increase of free amino acids throughout the entire gestation period, the dynamics of this process suggested a similar study on the dynamics of the human gestation process. Human amniotic fluid studied progressively throughout the gestation period, with the purpose of ascertaining the specific free amino acids present quantitatively, should prove to be a field for interesting information and comparisons.

It is evident that the rat mechanism does not hold for the human. Therefore, means should be evolved for studying the latter. This investigation, confined to the period of parturition, shows the relationships of three extracellular fluids, the relatively high concentration in fetal cord serum and maternal serum in relation to the amniotic fluid in humans, thus pointing to the placental mechanism. It is important to remember how greatly the rat placenta differs histologically from the human placenta, and consequently the reversal of free amino acid concentration will not be found surprising.

Chromatographic studies of human amniotic fluid, maternal and fetal blood serum at term present interesting contrasts to chromatographic studies

TABLE I. QUALITATIVE AND QUANTITATIVE FREE AMINO ACIDS IN MATERNAL SERUM, FETAL SERUM, AND AMNIOTIC FLUID

AMINO ACID	CASE 1			CASE 2			CASE 3			CASE 4			CASE 5			CASE 6			CASE 7		
	MS	FS	AF	MS	FS	AF	MS	FS	AF	MS	FS	AF	MS	FS	AF	MS	FS	AF	MS	FS	AF
Cysteic acid			2															2	3	3	2
Aspartic acid	2	4	5	3	4	6	2	3	3	5	2		3	3	3	3	3	3	3	3	3
Glutamic acid	1.5	8	3	2	7	2	2	6	2	2	20	2	2	6	2	2	3	3	2	3	2
Ornithine		3	3		4	3		3	3		3		3	3	3	2	2		2		
Carnosine																3	3	3	3	3	
Serine	6	7	2	2	6	2	2	7	1.5	2	5	2	2	2	2	2	2	1.5	2	2	1.5
Glycine	1.5	3	2	3	4	2	2	3	1.5	1.5	3	1.5	2	2	2	1.5	1.5	2	2	2	1.5
Threonine	5	11	3	6	9	3	6	10	2	2	10	2	2	2	2	2	2	2	1.5	3	1.5
Alanine	11	20	3	7	9	2.5	15	20	2	2	20	2	3	3	2	2	3	2	1.5	3	1.5
Lysine	5	20	6	3	7	3	3	14	3	2	6	2	3	5	3	3	3	3	2	5	2
Glutamine	14	15	3	13	13	9	6	11		2	3	2	2	2	2	3	2				
Hydroxylysine					2	2			3												
Arginine	2	3		2	2					2			3	2		2		2	2	2	1.5
Tyrosine		5	3	2	2	2	2	2	2		3	2	2	2		3	3	3	2	2	
Valine area	2	6	2	5	3	4	6	5	2	2	3	2	3	5	2	3	5	3	3	3	2
Leucine area	2	3	2	2	2	3	2	2	1.5	2	3	2	2	2	2	2	2	2	2	2	2
Total (gamma per 200 lambda)	52	108	39	53	74	43.5	48	86	26.5	24.5	81	19.5	32	39	25	33.5	34.5	31.5	31	36	20.5
Total mg.%	26	54	19.5	26.5	37	21.75	24	43	13.25	12.25	40 5	9.75	16	19.5	12.5	16.75	17.25	15.75	15.5	18	10.25

Material used: 200 lambda.

of rat amniotic fluid and maternal blood serum, and further suggest the value of additional studies on the three human extracellular fluids during the whole gestation process.

Summary

The concentration of free amino acids in human cord serum at the time of parturition is in every case examined higher than in the maternal blood serum and the amniotic fluid.

Specific free amino acids do not increase proportionally but show marked variability. The specific chromatographic analysis is presented.

I wish to thank Mr. Dean C. Altman, head of the Photographic Department of this Hospital, for the reproductions, as well as Mrs. Sharon D. Lundberg and Mr. Jimmy K. Tsujimura of our staff for their technical assistance.

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THE OXYGEN TENSION OF THE AMNIOTIC FLUID*

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THE possibility of studying the oxygen tension (pO_2) of the human fetus before birth is very limited. The only available method of obtaining an intrauterine pO_2 determination is to investigate the amniotic fluid. As the whole surface of the fetus is exposed to the amniotic fluid, the pO_2 of this fluid can be expected to bear an important relation to that of the fetus. In rabbits, the pO_2 of the amniotic fluid was measured by Campbell[2] but no analyses of the pO_2 of the human amniotic fluid seem to have been made.

Material

The amniotic fluid from 45 patients has been analyzed. In 18 cases the amniotic fluid was taken at or near term and in 27 cases the fluid was taken from women undergoing legal abortion.

In order to get another intra-abdominal pO_2 determination for comparison, the fluid from 10 benign ovarian cysts was taken. Cases 1 to 6 and 8 to 10 were follicle cysts and Case 7 a lutein cyst. They varied from the size of a walnut to that of a football.

At or near term the uterus was punctured percutaneously (in 7 cases) or during cesarean section (in 11 cases) after the abdominal wall had been opened. Before percutaneous puncture it may be necessary to ascertain by x-ray where the placenta is situated. If it is on the ventral side of the uterus no puncture should be undertaken. Sometimes it was very difficult or impossible to obtain the fluid, especially if the fetus was small and the amount of amniotic fluid scant. If the fluid was viscous and contained many cells, it often could not be used for pO_2 measurements with the dropping mercury electrode as the cellular agglomeration disturbed the regular flow of the mercury. Since we have the Clark electrode these cell-rich fluids also can easily be investigated.

With one exception, none of the punctures resulted in complications. One woman in whom a percutaneous puncture had been made complained of pains in the upper abdomen, but within half an hour these ceased. Probably she had a minor intraperitoneal hemorrhage caused by the needle in the uterine wall.

In the course of induced abortion, the uterus was either punctured after the opening of the abdominal wall, as in cesarean section, or the puncture was made through the anterior fornix of the vagina.

The ovarian cysts were punctured in the course of abdominal operations.

*This study has been supported by grants from the Association for the Aid of Crippled Children, New York.

Methods of Measuring the Oxygen Tension

The oxygen tension was measured polarographically. The analyses were at first done with the dropping mercury electrode (Methods I and II) by the standard technique for complete polarograms.[5] Later a Clark[4] electrode (Method III) was used at a fixed voltage. The polarograph is a LKB-Blomgren polarizer with a Leeds & Northrup Speedomax recorder.

Methods I and II.—Because of the variability in the physical properties of the amniotic fluid, the amount of dissolved oxygen, which is directly proportional to the pO_2, cannot be calculated directly or from a calibration line of general validity. Instead calibration points must be made on each separate sample. This was accomplished in two different ways:

1. By equilibrating the fluid with gas mixtures of known oxygen tensions. This was done in the first 15 cases.

2. By mixing the sample with 0.8 N potassium chloride aqueous solution of known oxygen tension (internal standard technique). This was used in 16 cases of amniotic fluid and in 8 of the cysts.

Methods I and II are discussed in more detail in another work.[6]

Method III.—The Clark electrode is very convenient for measurements of pO_2 in biological fluids. The calibration curve made on KCl solution or water is also valid for this fluid. The sample to be measured is introduced into a "cell" containing 2 ml. of fluid. Before being filled with the amniotic fluid, the cell is washed with a gas mixture which has a pO_2 of about the same magnitude as is expected in the sample. Alternatively, the cell may be washed two or three times with the sample itself. Measurements done without this washing will invariably be too high. This method was used in 14 cases of amniotic fluid and in 3 of the cysts.

With the Clark electrode it is possible to take a double reading of the pO_2 in the amniotic fluid in 5 minutes, whereas one single reading takes 60 minutes with Method I and 20 minutes with Method II.

The accuracy of Method I is of the order ± 4 mm., of Method II ± 2 mm., and of Method III ± 1.5 mm. Table I shows the results of repeated measurements with Method III. The maximum deviation is ± 1.5 mm. but the mean deviation is only ± 0.5 mm.

TABLE I. REPEATED pO_2 MEASUREMENTS ON THE SAME SAMPLES

	SYRINGE I				SYRINGE II	
CASE	A	B	C	D	A	B
1	9	8				
2	21	21	19			
3	11	11	10			
4	10	9				
5	11				9	8
6	4	4				
7	6	6				
8	8	8			7	5
9	16	16	13	15		
10	7	7				
11	9	8				
12	7	6			5	5
13	3				2	2
14	8	8	8		10	
15	24	25	25		29	28

Maximum deviation 3 mm. Mean deviation 1 mm.

It is obvious that for this type of pO_2 measurement the Clark electrode has great advantages over the dropping mercury electrode.

Results

The pO_2 of the 45 specimens of amniotic fluids is shown in Table II. The pO_2 varies between 1 mm. and 31 mm. Hg but most of the values are between 6 and 14 mm. (28 cases). Because of the very low oxygen capacity of the amniotic fluid, small air bubbles make big errors and on the basis of our present experience we suspect that the high values are due to technical errors.

TABLE II. CORRELATION OF THE OXYGEN TENSION IN AMNIOTIC FLUID WITH THE LENGTH OF GESTATION*

METHOD I		METHOD II		METHOD III	
GESTATION TIME IN WEEKS	pO_2	GESTATION TIME IN WEEKS	pO_2	GESTATION TIME IN WEEKS	pO_2
Induced Abortion.—					
10	7	12	14	17	11
		14	8	20	9
14	18	14	20	22	8
17	9	15	13	23	7
18	13	15	24	19 ?	16
18	19	15	14	20 ?	15
20	6	17	13		
20	7	17	4		
20	17	18	13		
22	1	20	13		
		20	31		
		18 ?	11		
Cesarean Section.—					
37	2			36 ?	25
38	8			39	10
40	10	40	14	39	4
40	7			41	2
43	6			41	8
Percutaneous Puncture.—					
40	7	40	15	34	20
		40	7	35	8
		40	13	40	9

*In some cases marked with ? it was not possible to establish the gestation time with accuracy.

The pO_2 of the 10 ovarian cysts is given in Table III. The fluid of some of these cysts had a notable oxygen consumption and corrections have been made for this. In the amniotic fluid, the oxygen consumption over a period of 1 hour is negligible.

TABLE III. THE OXYGEN TENSION OF BENIGN OVARIAN CYSTS

METHOD II		METHOD III	
CASE	pO_2	CASE	pO_2
1	47	8	41
2	39	9	44
3	42	10	33
4	43		
5	58		
6	41		
7	44		

Comment

The pO_2 of the ovarian cysts can be compared to that in the nitrogen bubble of Campbell,[2] who found a mean value of 40 to 50 mm. Hg intra-abdominally. Our values for the ovarian cysts are of the same magnitude and probably represent the intra-abdominal pO_2 in man. The pO_2 in the amniotic fluid is much lower and the mean value in our 44 cases is 11 mm. Hg. This value is very similar to that of Campbell,[3] who measured the pO_2 in the amniotic sac of rabbits. His values were between 3 and 33 mm. Hg with a mean value of 18 mm. Hg in 11 cases. Campbell made these analyses, too, with the nitrogen bubble technique.

The relation between the pO_2 in the amniotic fluid and that of the fetus is interesting and important. In 1957 we[6] reported experiments on the transportation of oxygen through the skin, using a modification of the Baumberger and Goodfriend[1] method of analyzing the arterial pO_2 through the skin of a heated finger. It was found that the arterial pO_2 equilibrates through the skin into a salt solution in which the finger is immersed. We therefore have reason to suppose that the oxygen tension of the amniotic fluid and the oxygen tension of the skin of the fetus are in equilibrium.

Oxygen can enter or leave the amniotic fluid through either the placenta or the layers of the amniotic sac or through the skin of the fetus. Possibly some oxygen is also consumed by the cells in the amniotic fluid but, if so, this consumption is very small as we have found. It is not possible to estimate how the pO_2 in the amniotic fluid is balanced, but because of the large surface of the fetus as compared with the other surfaces which are active in this respect, it is reasonable to assume that the pO_2 of the amniotic fluid will resemble the pO_2 of the tissues of the skin of the fetus.

The adult arterial pO_2 is about 100 mm. Hg. The venous pO_2 is about 30 to 50 mm. and the pO_2 of the intra-abdominal or subcutaneous tissues between 30 and 50 mm. The arterial pO_2 of the fetus is about 30 mm. and its venous pO_2 about 10 mm. Hg. From this it may be guessed that the tissue pO_2 of the fetus is also about 10 mm. Hg. As the values observed in the amniotic fluid are of this magnitude, it seems probable that these values also indicate the pO_2 in the skin of the fetus in utero.

In 5 cases, the pO_2 of the amniotic fluid was less than 5 mm. Hg. This is particularly interesting because these values suggest hypoxia of the fetus, but it is as yet too early to tell whether the measurements of the pO_2 of the amniotic fluid may be used to show intrauterine hypoxia.

Summary

The mean pO_2 of the amniotic fluid in 45 cases was found to be 11 mm. Hg and of 10 ovarian cysts 44.9 mm. Hg.

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PROLONGED PREGNANCY SYNDROME*

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RECENT interest in the prolonged pregnancy syndrome arises from the physiological studies of Barcroft and his colleagues[4] and from the clinical reviews of Clayton[12, 13] in England, of Rathbun[46] in the United States, of Hosemann[26] in Germany, and of McKiddie[34] in Scotland.

These pioneer studies, combining experimental physiology with clinical obstetrics, opened widely into the relatively unknown field of maternofetal relationships and their clinical importance. These studies have stimulated investigation along many lines. Such is the wealth of new information, most of it immensely valuable, which has arisen directly or indirectly out of their work, that we owe a great debt to these investigators.

The volume of experimental work continuing is such that our knowledge in this field, especially in late pregnancy and labor, is rapidly expanding.

It is time that the clinical syndrome of prolonged pregnancy is appraised in the light of experimental work, and of clinical experience over the last few years during which special study has been given to the problem. It is not yet time to make a final assessment of the clinical importance of this syndrome, since new facts are still emerging, especially with regard to methods of estimating the status of the baby at birth and to the long-term effects of anoxia.

The Syndrome Statistically

To the layman the words "prolonged pregnancy" imply that pregnancy in the human has a normal duration which can be defined so that durations outside certain limits can be classed as abnormal. Some European countries have set definite legal limits to the duration of pregnancy. To the legal mind such limits are tidy and certainly useful. It must be remembered that such limits extend from the last possible date of access. In countries such as Britain and the United States of America, where each case is assessed on its merits, the clinical and scientific evidence given in open court is often meager in the extreme. A final decision is based often on the legal virtue, by default of contrary evidence, of the lady concerned. By their very nature legal proceedings of this kind must never be taken, and ought not to be quoted, as a solution of the scientific or clinical problem as it faces the practitioner.

When the *scientist* studies the gestation period, he is first concerned with the problem of establishing a starting date. He finds that there are variations

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in the menstrual cycle, in the ovulation time, and in the luteal phase,[16, 22] and must consider even the possibility, in the human, of delayed implantation. He finds it difficult to begin his study at all if he cannot fix for himself an accepted criterion for the start of pregnancy.

In limited series this is of course possible. Stewart[50] showed that, calculated from ovulation time, the duration of pregnancy was limited to a fairly narrow range, although calculation from menstrual date in the same patients suggested grossly prolonged pregnancy.

If, on the other hand, the scientist is willing to accept the calculation of gestation period from the first day of the last menstrual cycle, so that he may study statistically large series, he will find that the duration of pregnancy in the human varies over a very wide range.

A fairly narrow range was considered normal by the physicians of antiquity. Despite the use of lunar months by some and solar months by others, it seems clear that Hippocrates, Ovid, and Virgil all accepted some little scatter of duration for pregnancy but that Pliny, at least, was a supporter of the possibility of protracted gestation. Nesbitt,[44] Strand,[52] and Higgins[23] have recently extensively reviewed the literature in this regard and it would be superfluous to attempt to improve on their bibliography.

It appears that, in healthy populations, the mean duration of pregnancy calculated from the first day of the last menstrual period is about 282 days.[28, 54] A shorter mean is of course found in populations with a high incidence of prematurity. The proportion of pregnancies which are prolonged beyond this mean time varies much in reported series. For example, between 22 and 24 per cent are reported as being prolonged after the two hundred and ninetieth day,[26, 28] and from 7 to 13 per cent prolonged after the two hundred and ninety-fourth day.[20, 26, 53, 60] The lower figures are more likely to be accurate since authors reporting these series took great care to exclude all doubtful cases. It is rarely realized that in most carefully studied series 15 to 18 per cent of the total cases must be excluded because of doubtful menstrual data. This is especially so in the young primigravida, in cases of illegitimate pregnancy, and in cases of prenuptial conception. The accurate calculation of the duration of a pregnancy in retrospect, i.e., after delivery, or from hospital records, is very difficult indeed and many series quoted are suspect from that viewpoint. Reasonable accuracy can be expected only where the patients are seen early in pregnancy and menstrual data checked at the first visit and assessed against the size of the uterus. This of course establishes only the "clinical" duration which is the problem we are discussing, and would not exclude delayed implantation or any such anomaly.

The Syndrome Clinically

To the clinician it is only too obvious that human pregnancy is of varying duration. The use of graphs, tables, curves, means, medians, and standard deviations tells us only what we already know.

The clinician, however, faced with the care of patients, has before him the disturbing entity of the "prolonged pregnancy syndrome." We clinicians

who accept this syndrome are often criticized by many, who quote to us irregularity of menstrual cycles, delayed ovulation time, and "standard" variations in gestational age. In this way we are expected to deny the existence of a real clinical entity which is associated with fetal disablement and death, leads many mothers into the greater risks of operative interference and delivery, and which on at least one occasion nearly caused the end of a Royal House.[25]

It is quite as illogical to discount the existence of a prolonged pregnancy problem by quoting the cases of one or two babies born alive after 330 days as to suggest that prematurity is not a problem since a few infants born before 190 days survive.

It is also illogical of course to allow to this syndrome a greater clinical importance than it deserves. In recent years this syndrome has collected unduly vociferous devotees and an equally ardent group who deny its existence. Somewhere in between lies the clinical importance of the syndrome.

What then is the syndrome?

Clinical Features

When compared with deliveries at or just before term, there is in prolonged pregnancy an increase in (1) perinatal mortality, (2) the incidence of fetal distress, and (3) the incidence of difficult labor.

Rise in Perinatal Mortality.—

The literature on the perinatal risk is enormous, ranging at least over the last 70 years from Hirst[24] and McKerron[33] to Strand,[52] Higgins,[23] and Tucker and Benaron.[56]

In 1954, reporting on deliveries in Aberdeen Maternity Hospital over the 4 years from 1948 to 1952, inclusive, I[60] found a statistically significant rise in the perinatal mortality from 1.2 per cent for deliveries in the fortieth and forty-first weeks of pregnancy to 2.8 per cent for deliveries during, or after, the forty-third week, i.e., after the two hundred and ninety-fourth day. The rise was due mainly, but not entirely, to a rise in stillbirths, and was seen mainly, but not entirely, in babies born of primigravidas.

The rise in perinatal mortality, due chiefly to an increase in stillbirths, had of course been reported by many previous authors from Ballantyne[3] in 1902 to Gibson[20] in 1952, and has of course been confirmed since by Strand,[52] Gibson,[21] Nesbitt,[45] and Cope,[17] from Scandinavia, Ireland, the United States, and Australia, respectively. In some series, notably recent American reports,[18, 56] no excess mortality is found in prolonged pregnancy.

Certainly in my experience and in that of most investigators in all parts of the world, this was a true finding. I say "was" advisedly because, as I will show later, modern obstetrics tends "inadvertently," if I may use the phrase, to destroy this picture.

The extra mortality in my cases was due partly to a rise in the incidence of deaths due to difficult labor and delivery, but mainly to deaths from anoxia where no obvious clinical feature of the pregnancy or labor could explain why such death occurred.

This was my main point, i.e., that the main increase was due to death from "anoxia" which was clinically unexplained. There was also a higher incidence, than at 40 weeks, of death from anoxia in association with difficult labor. Death from anoxia during difficult labor was an uncommon finding in deliveries before the two hundred and eightieth day.

TABLE I. THE INCIDENCE OF FETAL DISTRESS IN 6,189 PRIMIGRAVIDAS (SINGLE PREGNANCIES)

AGE OF MOTHER	WEEKS OF GESTATION										TOTAL	
	-38		39/40		41		42 AND LATER		UNCERTAIN			
	INCIDENCE %	TOTAL NO. OF PATIENTS	INCIDENCE %	TOTAL NO. OF PATIENTS	INCIDENCE %	TOTAL NO. OF PATIENTS	INCIDENCE %	TOTAL NO. OF PATIENTS	INCIDENCE %	TOTAL NO. OF PATIENTS	INCIDENCE %	TOTAL NO. OF PATIENTS
15-19	4.0	101	11.0	190	16.3	147	13.7	131	12.6	175	12.0	744
20-24	10.2	353	10.6	968	19.2	765	25.1	672	16.1	465	16.5	3,223
25-29	12.0	166	15.8	557	21.3	381	31.8	343	19.7	117	20.3	1,564
30-34	15.0	60	20.5	151	30.3	132	31.6	95	27.8	36	25.3	474
35+	17.9	28	21.0	57	36.5	52	56.0	25	18.2	22	29.3	184
Total	10.5	708	13.2	1,923	24.4	1,477	26.9	1,266	16.5	815	18.2	6,189

Am. J. Obst. & Gynec.
December, 1958

Many authors who admit a rise in perinatal mortality after term consider that this rise is due entirely to the increased mechanical difficulty of delivery and is not in any way contributed to by an inherent lack of resistance in the baby.

Gibberd,[19] Gibson,[21] Strand,[52] Nesbitt,[45] and Cope,[17] however, find that, in their series, the increased mortality is in great part due to death from anoxia rather than exclusively from the trauma of difficult labor.

Features of the Added Risk.—Some features of this increased risk are, however, worthy of comment:

a. The magnitude (or absence of magnitude): The increased rate in my cases was statistically significant. The extra risk to the baby born after the two hundred and eighty-seventh day is, in my cases, of the same degree as that quoted in the more recent literature; it is much less than the risk quoted originally in a selected group of cases by Clifford and associates.[15] The risk is however such that only 2 *extra* babies will die, in every 100 pregnancies which actually reach the two hundred and ninety-fifth day (i.e., 7 per cent of all pregnancies). If the babies delivered after the two hundred and eighty-seventh day are included in the prolonged pregnancy group, only 5 babies of every 1,000 total born to primigravidas were likely to die *of the risks peculiar to prolonged pregnancy.* This is about 12 per cent of the total perinatal loss in primigravidas.

The small magnitude of the risk was very clearly pointed out by Gibberd[19] but, of course, as emphasized by Clifford,[15] the risk is greater in selected groups. I[60] suggested from other evidence that the risk would, for example, be negligible in babies of young primigravidas and of most multigravidas, would rise steadily with rising maternal age, and would increase if associated with pre-eclampsia or threatened abortion earlier in the pregnancy.

b. The special cases: The extra risk to the baby in prolonged pregnancy is reasonably serious in some groups of patients and negligible, or nearly so, in others. The extra risk is borne by the babies of: (1) primigravidas as against multigravidas; (2) older primigravidas (over 30) as against young primigravidas; (3) primigravidas with some associated antenatal abnormality of the pregnancy, e.g., hypertension, pre-eclampsia, or previous threatened abortion.

The babies of *multigravidas* are at little risk but there are certain clinical groups in which a real risk appears, i.e., those with a history of: (1) stillbirth (at any stage of gestation) in the immediately preceding pregnancy, since the oxygen supply is impaired[64]; (2) false labor at or just after term[23, 42]; (3) antenatal abnormality as previously discussed, i.e., pre-eclampsia, previous threatened abortion, etc.; (4) dystocia due to the shoulders. I am rather of the same opinion, however, as expressed by Calkins[10] some years ago, that most very large babies who produce this problem are born before term.

Fetal Distress.—

Increased Incidence.—First clearly emphasized by McKiddie,[34] this has been confirmed frequently since.[48]

Pattern.—By gestational age: The incidence of fetal distress in primigravidas as pregnancy becomes prolonged is seen in Table I. The total incidence is 18.2 per cent in my series.

Maternal age: The rise in fetal distress by gestational age is independent of maternal age: For example, the incidence of fetal distress in the labors of primigravidas under 19 years of age after the two hundred and eighty-seventh

day was only 13.7 per cent as against an incidence of 56 per cent in the labors of 25 primigravidas over 35 years of age at the same period of gestation (Table I).

Type of labor: This rise in fetal distress is also independent of the type of labor. The rate in difficult labor rises more steeply in prolonged pregnancy.[60]

Cause.—Clinical fetal distress falls into two main groups: (a) cases where the passage of meconium is the first sign of distress, and (b) those in which the slowing of the fetal heartbeat is the first sign. As pregnancy becomes more prolonged there is a rise in the incidence of both clinical signs, but meconium, as a first sign, shows a more definite and steady increase through term. From my experience with my oxygen studies, this indicates that there is a greater incidence of cases of deficiency of transplacental oxygen transfer as pregnancy becomes prolonged. Slowing of the fetal heartbeat is (apart from cord involvement) in my experience almost always a pressure phenomenon in association with difficulty in labor, and the incidence of the former rises with that of the latter.

Whatever the cause of the distress, however, and whichever the type, the oxygen supply to the fetal heart muscle and brain is (at the time distress is manifest) very low.[62, 63, 64] As pregnancy becomes prolonged, therefore, more and more babies, especially of older primigravidas, are exposed to periods, long or short, when their oxygen supply is probably dangerously low, e.g., in the forty-third week half of the babies of primigravidas over 35 years of age would appear to be deficient in oxygen at some point in the labor. This is a very great problem in itself because of the possibility of long-term damage and is discussed in full elsewhere.[63, 64]

Difficult Labor.—

It has been shown by many authors[6, 13, 23, 46, 47, 51, 60] that in primigravidas the incidence of difficult labor rises steadily as pregnancy becomes prolonged. This increase is almost certainly due in great part to the increasing weight of the baby[27, 51, 61] and to an increasing head diameter.[31] Clinically, however, many labors after term seem to be characterized by dysfunction of uterine action with undue prolongation of the first stage. To what extent this dysfunction is due to associated minor disproportion, or to minor disproportion caused by malposition of the head, it is impossible to say. Whatever the cause, the incidence of serious difficulty in labor or delivery of primigravidas rises steadily, in my series,[60] from 3.1 per cent for deliveries in the fortieth week to 13 per cent for deliveries in the forty-second and later weeks

Death of the baby in association with difficult labor in the later weeks of a prolonged pregnancy was due to: (a) the inevitable risk of trauma; (b) an increased risk of anoxia, as a dysfunctional labor became prolonged; or (c) a combination of both, i.e., the greater risk of trauma in the already anoxic baby.

Summary to Date.—

There is general agreement in the literature, in cases where the gestational age of the pregnancy is clinically accurate, that:

1. There is a greater risk to the baby mainly of stillbirth, and that the *extra* risk of death is borne by about 2 per cent of babies delivered in the period from the forty-second week onward, or about 5 babies in every 1,000 born.

2. That the risk is due mainly to death from anoxia but a fairly large proportion of deaths occurs directly because of difficult labor. A few of the deaths from anoxia occur before the onset of labor but more early in the course of a normal labor.

3. There is a greatly increased risk that the baby will be called upon to sustain anoxia of quite severe degree, manifest by fetal distress, but which it will usually survive.

4. That the baby is more likely to be called upon to sustain a difficult labor.

5. That the risks, as above, are very small indeed in some groups of patients and show little if any increase from the risks at term, but that in other groups of cases the risks assume significant proportions.

The Likely Oxygen Pattern

I would like at this stage to discuss briefly the oxygen levels in the blood in the umbilical vessels in babies from prolonged pregnancies. They follow very closely the known clinical pattern of the syndrome. In any series of course certain cases must be excluded from the study as they will show abnormal oxygen readings for other reasons, as discussed in full elsewhere[62, 63, 64]: (a) fetal distress due to cord strangulation, (b) fetal distress with slowing of the fetal heart as a first sign, (c) difficulty in extraction of the baby, preceding sampling of the blood, and (d) anesthesia with added oxygen or cases with anesthetic difficulty.

In addition, all other anoxia-producing hazards, such as pre-eclampsia, previous threatened abortion, previous stillbirth or neonatal death, difficult anesthesia, etc., must be specially noted, as they themselves will depress readings.

In the cases of young primigravidas and multigravidas with a previously normal history, the per cent saturation with oxygen of the blood in the umbilical vein will not fall, to any degree, as pregnancy becomes prolonged (i.e., the blood in the umbilical vein will remain 50 to 60 per cent saturated with oxygen) although the oxygen capacity may rise. In other words, the altitude response will be adequate. The baby is no more liable to the risks of anoxia than at term, although unduly traumatic labor might kill it.[35, 64]

Where primigravidas over 25 years of age have been studied as a group,[36, 57] there is a definite fall in the mean saturation of the blood in the umbilical vein to about 40 per cent after the forty-first week and some, at least, of the babies would be at serious risk of death from anoxia and would be less able to withstand difficult labor.

If the pregnancy is complicated, e.g., by pre-eclampsia, which will of itself decrease the transfer of oxygen, then the risks are increased and become real in the young primigravida and in the multigravida, and could be severe in the older primigravidas.[32, 60, 65]

Where the history of a multigravida shows fetal death in the immediately preceding pregnancy the oxygen level is low at and after term.[64]

Much of the difference in the findings of the various investigators with regard to oxygen levels can be explained by the age and parity distribution of the patients and by the exclusion or otherwise of cases of clinically abnormal pregnancy, of cord anomalies, and of fetal distress with heart slowing as a first sign.

In recent years confirmation in another way has been obtained by studies of placental blood flow and uterine muscle flow. The most applicable studies are those of Browne and Veall,[8] Moore and Myerscough,[40] and Browne.[9]

These show quite clearly a decrease in clearance of radioactive sodium from placental pool and uterine muscle in cases of prolonged pregnancy, more marked in primigravidas.

The study of Moore and Myerscough[40] in particular shows clearly the effect of maternal age and parity, gestational age, and pre-eclampsia. It is seen here that the rate of uterine muscle flow deteriorates with rising maternal age and rising gestational age independently in primigravidas and is of course much

worse if pre-eclampsia (even without albuminuria) is superimposed. Browne[9] from further studies has shown that there is a deterioration in *placental* blood flow in cases of prolonged pregnancy.

Therapy

Difficult Labor.—

I have already stated that I had been discussing the pattern of perinatal mortality up to 1952 and that modern obstetric techniques were inadvertently destroying the pattern. This is essentially because of the modern treatment of prolonged and difficult labor with much earlier recourse to cesarean section.

The great majority of difficult labors occur after the end of the fortieth week and many of the deaths of babies after this time are associated with prolonged or difficult labor, especially those of older primigravidas. Since, in the last few years, in every country, there has been a great rise in the cesarean section rate in difficult labor, especially in the older primigravidas and especially in the presence of fetal distress, many babies in the prolonged pregnancy group have been automatically saved.

As an example of this even some years ago, we see that in Aberdeen, in primigravidas delivered between 1938 and 1947, inclusive, 22.9 per cent of all perinatal deaths occurred in babies delivered after the two hundred and eighty-seventh day and over 1 per cent of all primigravidas lost a baby because of the problems of prolonged pregnancy. In deliveries between 1948 and 1952, inclusive, only 15.5 per cent of perinatal deaths occurred after the two hundred and eighty-seventh day and less than 6 per thousand babies of primigravidas were lost in the prolonged pregnancy.

In 1954, I[60] outlined my views on the clinical management of difficult labor in prolonged pregnancy, with special reference to the prevention of fetal death from anoxia, and stressed the clinical significance of meconium staining in the liquor.

From my experience in Britain and in the United States, it appears that similar views are held in most clinics, and that in recent years labors complicated by uterine dysfunction and mechanical difficulty are now terminated much sooner and often before fetal distress is manifest. Such a clinical development has automatically saved more than half the babies previously lost as part of the prolonged pregnancy syndrome.

There still remains the problem, however, of the "unexplained" deaths from anoxia.

The fetal loss in this group is very small indeed and while admitting that the risks exist we clinicians are acutely concerned with the alternative risk of interference.

Induction of Labor.—

In 1954, I[60] suggested that such deaths could be prevented only if labor and delivery could be achieved at a period of gestation when the oxygen supply to the individual baby was still good. This depended of course on a safe and successful method of induction of labor.

In 1952 we had in Professor Baird's unit in Aberdeen introduced a policy of routine induction of labor in primigravidas over 25 years of age when we were satisfied that the pregnancy had proceeded at least to the two hundred eighty-seventh day and the baby was of reasonable size. I must make two points clear here: first, that we considered such a policy indicated in this group only, i.e., 7 per cent of all primigravidas (there was no question of "wholesale induction" as is often suggested); and second, that we did not advocate its general use, but said only that we had introduced it in that unit and that "a longer period would be necessary before the role of induction could be clearly defined and the risks of the procedure properly evaluated."

We are now in a better position to evaluate the effects of this policy.

Sequelae of Induction.—It is not sufficient to evaluate induction only in the cases where prolongation of pregnancy is the only clinical abnormality. We must also consider the effects of induction in cases where pre-eclampsia and hypertension or other minor abnormality complicate the case of prolonged pregnancy. A policy of routine induction of course leads to induction even in cases with the possibility of slight disproportion which could produce an added complication.

It is clear therefore that a true picture can be obtained only if we consider all patients in whom labor was induced, for whatever reason, after the two hundred eightieth day. Indications in the given case are often multiple and all may not always be recorded. Even though indications might be labeled "routine" there was occasionally some very mild hypertension or suspicion of clinical disproportion.

I must emphasize that at this period the routine method of induction was by rupture of the hindwaters with a Drew Smythe catheter, a method rarely used in the Americas and singularly less efficient than forewater rupture. In the period studied accessory methods of induction, e.g., Pitocin, were rarely, if at all, used.

Results.—There were from 1948 to 1954, inclusive, 2,743 single pregnancies in booked primigravidas domiciled in the city of Aberdeen in whom the gestational period was known to have passed the two hundred eightieth day. Of these there were 462 primigravidas (12.8 per cent) in whom induction of labor was attempted. In 44 cases the forewaters were ruptured and in 418 the hindwaters. In 8 of the latter cases the state of the cervix was not recorded at the time of induction. In 132 of the hindwater cases the cervix was considered to be unripe, i.e., the cervix was firm, long, not taken up, and a finger was inserted with difficulty. Occasionally the cervix was so firm that the Drew Smythe catheter alone could be inserted. In 278 cases the cervix was considered to be ripe and "favorable" for induction. There were in all 8 elective cesarean sections performed and these have been omitted from the tables calculating time to onset of labor.

The time taken to go into labor: This depended, as seen in Table II, on:

(1) The method of induction: The number of cases of forewater rupture is small, but the great majority of the patients were in labor quickly, no matter the state of the cervix.

TABLE II. INTERVAL BETWEEN RUPTURE OF THE MEMBRANES AND THE ONSET OF LABOR IN PRIMIGRAVIDAS (INDUCTION AFTER THE TWO HUNDRED AND EIGHTIETH DAY)

METHOD OF RUPTURE OF MEMBRANES	TOTAL CASES	INTERVAL BEFORE GOING INTO LABOR (IN HOURS)						
		12	24	48	72	96	120	FAILED
Forewaters	44	70.5	79.7	95.4		100		0
Hindwaters (all cases)	410	40.6	60.1	78.1	87.6	93.7	95.4	4.6%
Ripe cervix	274	45.6	65.7	82.5	92.0	96.0	97.1	2.9%
Unripe cervix	129	30.2	49.6	69.0	78.3	89.1	92.2	7.7%

(2) The state of the cervix at the time of induction (hindwaters): It is notable that after 48 hours more than 80 per cent of the patients with a "ripe" cervix at the time of induction were in labor as against only 70 per cent of those with an unripe cervix. It is also important, however, to realize that, *despite*

an unripe cervix, 50 per cent of the patients were in labor within 24 hours and 70 per cent within 48 hours, though such a clinical state is considered unfavorable for induction.

(3) Maternal age at the time of induction (Table III): It is an extremely interesting finding that there is a clearly decreasing efficiency with rising maternal age. This is not clearly related to the state of the cervix at the time of induction. The numbers in the oldest age group are small and of doubtful statistical significance.

TABLE III. THE EFFECT OF MATERNAL AGE ON THE INTERVAL BETWEEN RUPTURE OF THE HINDWATERS AND THE ONSET OF LABOR IN PRIMIGRAVIDAS

MATERNAL AGE	TOTAL CASES	% WITH RIPE CERVIX AT TIME OF INDUCTION	% IN LABOR WITHIN 24 HOURS	% NOT IN LABOR AFTER 72 HOURS
-19	40	30	70	7.5
20-24	189	35	61	12
25-29	111	25	63	13
30-34	41	31	50	17
35+	22	48	39	17

The Incidence of Cesarean Section After Induction.—In this series the incidence was much increased (Table IV). It is of course true that the cases in which labor was induced were to some extent abnormal but the incidence of 10.3 per cent (43 operations) is high. In 3 of the cases the state of the cervix at the time of induction was not recorded.

TABLE IV. MAIN INDICATION FOR CESAREAN SECTION AFTER INDUCTION OF LABOR BY RUPTURE OF HINDWATERS AFTER THE TWO HUNDRED AND EIGHTIETH DAY OF PREGNANCY IN PRIMIGRAVIDAS

	SPONTANEOUS ONSET		INDUCTION WITH RIPE CERVIX		INDUCTION WITH UNRIPE CERVIX	
INDICATION	%	NO. OF CESAREAN SECTIONS	%	NO. OF CESAREAN SECTIONS	%	NO. OF CESAREAN SECTIONS
Dysfunction	1.1	25	1.8	5	2.3	3
Mechanical	1.4	31	1.4	4	6.8	9
Fetal distress	0.2	5	2.9	8	3.0	4
Other	0.6	13	1.1	3	3.0	4
All cesarean sections	3.2	74	7.2	20	15.2	20
Under 25 years	1.5		4		12.6	
Over 25 years	6.3		11		23.3	
Total no. of cases	2,281		278		132	

Incidence by interval before the onset of labor: While there was no relation between the time taken to go into labor and the length of the subsequent labor, the incidence of cesarean section rose the longer the delay before the beginning of labor.

In the cases of *ripe* cervix the incidence of cesarean section in patients who were in labor within 24 hours was 3.9 per cent, in those in labor after that time, 7.1 per cent. With an unripe cervix at the time of induction the rates were 12.1 per cent and 14.5 per cent, respectively. Especially in the unripe cervix cases the rate tended to continue to rise, the longer the delay.

Clinical factors affecting incidence: The incidence of cesarean section was greatly influenced by certain clinical factors operative at the time of induction.

(1) The age of the patient (Table IV): The increased incidence in primigravidas over 25 years of age is seen also after the spontaneous onset of labor.

(2) The state of the cervix at the time of induction (Table IV): It is clear that when the cervix is ripe (and despite the inclusion of some abnormal cases in the induction group) extra cesarean sections are mainly indicated because of heavy meconium staining of the liquor at the time of induction. This policy[57, 60] is, I consider, lifesaving to the babies of primigravidas over 30 years of age. It was in such cases that immediate operations were performed. This type of case is discussed more fully later. There is also in the "ripe" cervix cases some increase in the incidence of operations for dysfunction.

Where, however, the cervix is unripe at the time of induction there is a greatly increased cesarean section rate. This is due to a greater need for operation in cases of mechanically difficult labor (the "major mechanical," "major mixed [mechanical]" and "major mixed [equal]" groups of Stewart and Bernard[51]). There is also a slight increase in the need for cesarean section because of uterine dysfunction.

(3) Maternal height: In view of the apparent increase in the incidence of cesarean section because of difficult labor there ought to be a clear gradient of incidence when the cases are studied in relation to maternal height since, as shown by Bernard,[5] pelvic brim contraction is clearly related to height. The relationship is seen in Table V. When the mother was 5 feet, 4 inches or more, in height, no cesarean sections were required after induction because of difficult labor, and only 3 altogether in 108 patients. At the other extreme, of 25 patients under 5 feet, 1 inch in height, with an unripe cervix at the time of induction, cesarean section was needed in 8 (32 per cent).

TABLE V. INCIDENCE OF CESAREAN SECTION BY MATERNAL AGE AND HEIGHT AFTER INDUCTION OF LABOR BY RUPTURE OF THE HINDWATERS AFTER THE TWO HUNDRED EIGHTIETH DAY OF PREGNANCY IN PRIMIGRAVIDAS

MATERNAL HEIGHT	MATERNAL AGE: UNDER 25 YEARS — NO. OF CESAREAN SECTIONS	MATERNAL AGE: UNDER 25 YEARS — NO. OF PATIENTS	MATERNAL AGE: OVER 25 YEARS — NO. OF CESAREAN SECTIONS	MATERNAL AGE: OVER 25 YEARS — NO. OF PATIENTS	TOTAL — NO. OF CESAREAN SECTIONS	TOTAL — NO. OF PATIENTS	CESAREAN SECTION RATE %	
Unripe Cervix.—								
-5′0¾″	5	15	3	10	8	25	32	15.2
5′1″-5′3¾″	4	44	6	27	10	71	14.3	
5′4″+	1	20	1	16	2	36	5.5	
Cesarean section rate (%)	12.6		23.3		15.2			
Ripe Cervix.—								
-5′0¾″	1	40	6	26	7	66	10.7	7.2
5′1″-5′3¾″	5	77	7	63	12	140	8.6	
5′4″+	0	34	1	38	1	72	1.4	
Cesarean section rate (%)	4.0		11.0		7.2			

I cannot explain this finding. Certainly the incidence of cesarean section is high in women under 5 feet, 1 inch, under any circumstances, and in quite a few of these cases there was clinical disproportion at the time of induction, so that the incidence of 10.7 per cent in patients with a ripe cervix is not out of place. The much higher incidence in short women with an unripe cervix and the clear pattern that runs through the whole table suggest, despite the small numbers, that unripeness of the cervix is related to subsequent difficulty in labor and will accentuate "mechanical" disproportion.

It has been suggested by Browne[7] and Latto,[30] among others, that a high fetal head or a head in the occipitoposterior position might be a direct cause of prolongation of the pregnancy. The idea is that failure of distention of the lower uterine segment might delay the onset of labor.

In my series unripeness of the cervix is not in any way related to the height of the patient and therefore it is unlikely that pelvic brim contraction is related. Moreover, the strong suggestion of our figures is that unripeness of the cervix (and usually as well an undistended lower segment) is independent of pelvic contraction and therefore a primary problem in itself. In other words, in many cases the head has failed to descend or flex well because the lower segment is firm rather than vice versa. Certainly in the patient with some disproportion an undistended lower segment added difficulty in labor.

It is clearly seen that all the patterns by height, maternal age, and state of the cervix are independent of each other and therefore additive.

The Liquor at the Time of Induction.—Meconium staining of the liquor was found at the time of induction in 46 cases, i.e., nearly 10 per cent of the cases where induction was performed in primigravidas after the two hundred eightieth day. It is interesting to study the method of handling these cases and the results achieved. There were 7 primigravidas over 30 years of age. In 3 immediate elective cesarean section was performed, in one operation was performed early in labor when slowing of the fetal heartbeat occurred, and in 2 others because of difficult labor with increasing meconium staining—6 cesarean sections altogether. In the remaining case labor began within half an hour and was completed within 13 hours by forceps delivery because of marked slowing of the fetal heartbeat with the onset of the second stage. The other 39 primigravidas were under 30 years of age. In these there were 2 immediate cesarean sections and 3 later. No babies were lost. Of the 35 babies delivered vaginally, however, 7 were in poor condition at birth, as were 2 of the 5 babies delivered by cesarean section after variable periods in labor. It is difficult to believe that some permanent damage might not have occurred to some of those 9. I consider that in primigravidas over 30 immediate elective cesarean section is indicated and that our good results are obtained only by this action. In younger primigravidas, short and easy labor will usually allow a live baby.

It is perhaps difficult to reconcile our oxygen findings[60, 63] in cases of meconium staining with the findings here. We lost no babies but in those delivered after labor 25 per cent were in poor condition. Survival of the fetus is not necessarily obstetrical success! High concentrations of oxygen were given to most of the mothers in labor and this may have helped; moreover normal easy labor does not depress the oxygen levels further and such babies therefore may survive labor despite initial oxygen levels in the lowered ranges I found when meconium staining is recent.

No Liquor at Induction.—I would like, however, to draw attention to a serious clinical syndrome. I[60] have already said that special attention should be paid to cases with "clinical" disappearance of liquor. In 33 (7 per cent) of our total cases of induction, less than 2 ounces of clear liquor and often sticky mucus only were obtained at induction. Of these, 6 were delivered by cesarean section because of marked fetal distress (meconium or heart) in labor but despite this 5 babies were lost. In 3 intrapartum death occurred in early labor without further signs of distress. One died neonatally as a result of gross intrauterine anoxia and the fifth was stillborn following a difficult forceps delivery. In 3 of the first 4, labor did not begin till more than 48 hours after rupture of the membranes. In 20 of the 33 cases marked fetal distress occurred in labor.

Fetal Distress After Induction.—There is after the induction of labor an increase in the incidence of fetal distress. This has been fully discussed elsewhere.[63]

Infection After Induction.—In this series the incidence of puerperal morbidity was exactly the same in cases where labor was surgically induced and in those where the onset of labor was spontaneous, and there were very few cases indeed of intrapartum pyrexia. One baby was lost, however, as a direct consequence of infection following induction.

In very recent years in many clinics the problem of infection after induction has become more serious.[48] It has reached a stage in some clinics where the infection risk is, itself, a limiting factor in the consideration of induction of labor for any reason. It is, of course, not a special problem of prolonged pregnancy.

Care of the Individual Patient.—In view of the information available it is possible to suggest therapy. Methods will change as new techniques become available and useful methods may become dangerous as new problems, e.g., infection, appear. I agree that this and any other problem of transplacental transfer will be nearer to solution in the individual case only once a method of measuring such transfer in the individual pregnancy is available.[14] As it is at the moment we have neither a method of assessment of the individual case nor a safe and sure method of inducing labor.

In labor: I[60] have fully discussed elsewhere the care of the prolonged pregnancy patient in labor and briefly discussed in this paper the success obtained by the modern attitude toward difficult labor. I would like to reiterate however the value of a hindwater "tap" with a Drew Smythe or male metal catheter in cases of difficult labor after term. This allows inspection of the liquor for meconium and therefore an assessment of the fetal response to the labor.

Before labor: This is the problem which concerns us all. I have earlier discussed special risk cases and cases with little or no fetal risk. I have shown what, in our experience, follows induction of labor by the techniques used by us. With this information at my disposal I can now present my personal views on therapy.

1. In the primigravida under 30 years of age with a clinically normal pregnancy and in the normal multigravida with a normal history (except perhaps where there has been a long delay between babies[23]) there is a minimal risk to the fetus. The risk is so small that there is no justification for induction of labor by our present methods on the sole indication of "the dates." The onset of labor can be awaited without worry provided that a high standard of antenatal care has excluded clinical abnormality, especially of the types of the special risk group (e.g., hypertension, pre-eclampsia, previous threatened abortion) and none of the signs of "postmaturity" are present.

2. In primigravidas or multigravidas with hypertension or clinical pre-eclampsia or previous threatened abortion, induction will mostly have been performed before term but, where this has not been done, or such complicating factors appear after the two hundred eightieth day, induction of labor should be considered.

3. In multigravidas with a history of stillbirth or early neonatal death in the previous pregnancy, *for any reason,* normal clinical practice should insist on delivery before, and often long before, term. Such cases should not be met in the prolonged pregnancy group. Similar action is indicated if the history tells of a difficult labor "after term" with a seriously distressed or damaged baby. If such a case is first seen however, after term, interference is imperative.

4. If the patient is a primigravida over 30 years of age, I do not think the pregnancy should be allowed to proceed longer than 290 days. (In many patients there will be an added factor, e.g., hypertension.)

5. What of the patient with clinical disproportion at, or after, term? Here we must remember that the longer the pregnancy proceeds, the greater will become the disproportion and the baby will become less and less able to withstand a difficult labor or delivery. This has been well discussed by MacLennan.[37] Especially when the cervix is ripe, it is often better to precipitate labor than to await its spontaneous onset one or 2 weeks later. Certainly the baby will be less likely to be oxygen deficient, and vaginal delivery can often therefore be achieved, since in the absence of fetal distress a longer period of trial labor can be allowed.

Clinical "Postmaturity"

I have talked in general terms of cases where there is evidence that anoxia due to prolonged pregnancy has added to it the risk of anoxia from disease or of the case of the older primigravida where in general the oxygen levels in the baby may be low. I would like now to mention three clinical "postmaturity" groups:

1. Patients, usually multigravidas, admitted at or after term in "false" labor. I induce "true" labor in these cases. The risks here have clearly been pointed out by Munro Kerr[42] and Higgins.[23]

2. Patients with clinical disappearance of the liquor amnii. This is probably the "postmature" group in the true sense. Certainly the babies of such patients are at a real risk and induction is indicated.

3. Patients who have shown a steady failure to gain weight (apart from intercurrent illness or dieting) for the previous 3 or 4 weeks, or who after the fortieth week show a steady fall in weight. Such patients often show clinical disappearance of liquor as well. The babies of such patients are at risk and induction is indicated.[60]

Interference

I have made such remarks as "interference is indicated" or "induction is indicated" in certain cases. The number of such cases will not be large but the incidence will depend on the number of elderly primigravidas and the frequency of complications, hypertensive disease, etc., in the unit concerned. Some units may find that only 2 per cent of their prolonged pregnancy patients come into the "risk" group, others, 20 per cent.

The method of interference indicated will again depend on the age and the height of the mother, the state of the cervix, the severity of complicating disease, the past history, the degree of disproportion, and the infection risk in the unit concerned. In many cases of this problem the obstetrician will, knowing the fetal risk, prefer (e.g., in the young, short woman with an unripe cervix) to await a little longer the spontaneous onset of labor.

Each case must be treated as an individual problem and assessed on its individual merits. It is worth remembering, for example, that in mild pre-eclampsia bed rest alone will improve uterine blood flow[41] and such action may allow us to await for a few more days the spontaneous onset of labor, again in the young patient, and especially if the pre-eclampsia is of short duration.[32]

Much has been said and much written against the unripe cervix. Certainly induction is less efficient and labor often difficult. Because of this, rupture of the membranes in such cases needs a stronger indication. However, an unripe cervix should never preclude rupture of the membranes if induction

is imperative, as frequently (especially in tall women) safe, rapid, and successful vaginal delivery can be achieved. There is much to be said for "trial of induction" in such cases. The problem of the unripe cervix is, as I have shown, mainly the problem of difficult labor, especially in the shorter woman, and cesarean section is needed only in such cases.

In some of the special risk cases we may await the onset of labor knowing the risks. In others elective cesarean section may be justified. In most cases, however, induction will be indicated about the two hundred ninetieth day. When this is so the best results should be achieved by rupture of the forewaters (under anesthesia if necessary), coupled with the previous use, or the use after 12 to 24 hours, of Pitocin by intravenous infusion in physiological dosage.[55] In the vast majority of such cases labor will have begun within 48 hours.

In a unit where there is a high incidence of infection after rupture of the membranes induction may be contraindicated or routine antibiotic or chemotherapy justified, at least after 24 hours.[11, 37, 38] It is probably unjustifiable for both obstetrical and psychological reasons in most of such cases in primigravidas to attempt to induce labor by rupture of the membranes, give Pitocin drip, and then be unwilling to perform an elective cesarean section if labor has failed to ensue within a reasonable time. In most such cases, however, if induction is considered justified on a careful consideration of all the factors in the individual case, then probably cesarean section after a reasonable time is also justified. This situation has been well discussed by MacLennan[37] and Baird.[2] Certainly if at induction there is little or no liquor, or meconium is found, it is imperative that delivery be achieved within 48 hours.

In units where all induction is routinely by Pitocin infusion *without* rupture of the membranes, it is extremely important in the prolonged pregnancy risk case that the membranes be ruptured after about 12 hours in labor so that the cases with meconium in the liquor can be recognized and an adequate knowledge of the fetal state be obtained.

Conclusions

We must acknowledge the existence of this syndrome. I have tried to define it and to assess its place in our experience. The outlook of each obstetrician will be modified by the type of his practice and by his own experience.[1, 29] There is no magical significance about the two hundred eightieth day or the two hundred eighty-second day or the two hundred ninetieth day. There is, however, an increasing problem as pregnancy becomes prolonged after about the thirty-ninth week, which is a different problem from those which confront the obstetrician, the mother, and the baby before that time. It has always to be remembered that, despite a low mortality the baby from the prolonged pregnancy will be more liable to oxygen deficiency indicated by fetal distress and be called upon to withstand a difficult labor. Both these factors, often additive, may cause minor damage with permanent sequelae. This is, however, another story, the study of which is just beginning.

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Discussion

DR. EDWARD H. DENNEN.—Complications are common in prolonged pregnancy. They may be severe enough in themselves to cause fetal death or neonatal death but even the mild types, when added to any hypoxia which may be present, can be fatal.

During the past 10 years at the New York Polyclinic Hospital, in 12,940 viable births, there were 267, or 2 per cent, with the gestation listed as 43 or more weeks. The fetal and infant mortality for the total 12,940 viable births in this series was 1.9 per cent, whereas there were 13, or 4.8 per cent, fetal and infant deaths in the 267 prolonged pregnancies. There were 11 stillborn infants, 6 of whom were macerated, and 2 neonatal deaths. One of the latter was that of a twin who died of adrenal hemorrhage after a breech delivery. The other was due to a congenital diaphragmatic hernia. In the stillbirth group, the causes of death were: toxemia 2, dystocia 2 (one, a transverse presentation with prolapse of arm and cord, the other, prolonged labor with a difficult forceps delivery), congenital anomaly 1, and placenta previa 1. Of the remaining 5 cases 4 had cord complications, 3 of the infants being macerated. The fifth was an 11 pound baby born spontaneously with intrauterine asphyxia the only cause of death found. Of the 4 with cord complications, one was a 9½ pound stillborn infant delivered spontaneously with two tight loops of cord about the neck; the other 3 were delivered spontaneously with the cord looped about the neck, tightly in 2 cases, and in one of these it was also around the shoulder.

It appears that very few of these cases could be interpreted as the postmaturity syndrome. This tends to support our opinion, which is so well expressed by Nesbitt in his recently published book, *Perinatal Loss in Modern Obstetrics,* as follows: "It would appear that too much stress has been placed on the fetal hypoxia concept to the complete neglect of other factors which might account solely or in part for the increased fetal mortality of postmature fetuses." It is quite apparent that this statement does not apply to Dr. Walker, as he emphasized the complications of pregnancy.

DR. R. GORDON DOUGLAS.—We have not had the same experience as the author with postmature babies. Our mortality rate in this group is not significantly different from the average for term infants. In this respect our figures agree pretty well with those of many American reports which have the over-all effect of minimizing postmaturity as an important complication of pregnancy.

We do have more fetal distress in these cases, however, and perhaps one of the reasons for the fact that the mortality rate in the postmature group is not above average is the increased number of cesarean sections that are done. This is a point that is now under study in our department.

THE NASAL MUCUS SMEAR IN TOXEMIAS OF PREGNANCY

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ABOUT three decades ago Harding and Van Wyck[1] treated patients suffering from various grades of toxemia of pregnancy by intravenous administration of 300 ml. of a 6 per cent sodium chloride solution. The results were disastrous: one patient who received two such injections became worse and eventually had a convulsion.

Dieckmann,[2] on the other hand, using a similar but slightly modified method was able to differentiate between patients with true pre-eclampsia-eclampsia and those with hypertension and kidney disease. Patients were given 1,000 ml. of 2.5 per cent sodium chloride solution, intravenously, over a period of 30 to 40 minutes. A retention catheter was inserted before the injection and drained 15 minutes after the completion of the injection. Two one-hour specimens of urine were collected for the determination of the concentration of sodium chloride. The patient with true pre-eclampsia retained much more sodium chloride than the one with pseudopre-eclampsia (hypertension or nephrosis or both). This test is based upon the decreased ability of the kidneys to concentrate sodium chloride in pre-eclampsia-eclampsia.[3] Body weight, edema, and blood pressure increased markedly upon salt infusion and on repeated injections proteinuria increased to values as high as 25 gm. per 24 hours.

A possible explanation for these observations is that among pregnant women who are apparently normal during early pregnancy, there are some who are potentially pre-eclamptic. This was postulated by Dieckmann[4] and confirmed by others. The statistics of the Department of Obstetrics and Gynecology of the University of Chicago Lying-in Hospital favor this hypothesis. There was a significantly greater weight gain in the patient with mild as well as with severe pre-eclampsia between the thirteenth and twentieth weeks of pregnancy than in the normal or hypertensive pregnant patient.

Likewise, weight gain might be the only abnormality present in the third trimester. Eclampsia has been known to occur sometimes without the development of proteinuria or hypertension.

Edema, therefore, is one of the principal diagnostic signs of the pre-eclamptic state. Although this may be the usual occurrence it is possible for true pre-eclampsia to occur with no pitting edema and only excessive weight

gain. This weight gain is usually too rapid to be accounted for by the growth of the fetus or the gravid uterus or other organs. Attempts to analyze the subcutaneous and muscle tissue and to study plasma, extracellular and total body water have been without success.[4] These findings indicate that perhaps an intracellular accumulation of fluid occurs in pre-eclampsia. Leg and thigh fluid volume studies[4] indicate that the volume can be increased by 50 per cent (5 L.) in some patients with no evidence of edema. The individual can retain 3 to 6 or more kilograms of water before any clinical edema is detectable in the ankles.

Normal pregnant women are known to have delayed water excretion, a condition which denotes a marked activity of the antidiuretic hormone (ADH) of the posterior pituitary. Similarly, normal pregnant women are known to have a certain degree of sodium chloride retention. This may denote some increased activity of the adrenal cortical hormones. The reabsorptive mechanism of the renal tubules is under the control of both the adrenal cortex and the antidiuretic hormone. Whether the derangement takes place in one before the other or in both simultaneously is unknown. Whatever the sequence of events is, the end result is retention of both water and electrolytes. This derangement becomes aggravated in pre-eclampsia-eclampsia.

In the past such storage of water and sodium chloride without obvious edema was difficult to understand. Today, with all the evidence in favor of the ability of sodium to replace intracellular potassium, the latter being excreted, occult edema can be explained. In other words, one expects sometime during the course of pre-eclampsia-eclampsia to find a change in the ratio between sodium and potassium excreted in urine and other body fluids. Potassium excretion in urine has been studied.[2] It did not, however, prove of practical value. There was no characteristic curve for pre-eclampsia or hypertension.

The purpose of this report is to present an illustration of the value of the nasal mucus smear in the study of toxemias in pregnancy. This method is useful in the detection of the true pre-eclamptic state and makes possible the avoidance of unnecessary premature terminations of pregnancy. This report also describes a simple procedure for detecting early changes in the excretion ratio of sodium to potassium.

Materials and Methods

In a preliminary study, nasal mucus smears were made on 5 patients at the Demerdash Hospital, Cairo University, Egypt: 3 in the pre-eclamptic phase and 2 in eclamptic convulsions, according to the procedure previously described by the senior author.[5]

The excretion of sodium and potassium in the nasal and cervical mucus of normal pregnant women was studied in this laboratory in an attempt to relate the sodium and potassium excretion to the fern phenomenon. Difficulties, however, were encountered in the collection and accurate measurement of the size and weight of the sample. As a consequence, some of the mucus, as obtained, was spread on a slide for the fern test while the remainder was

TABLE I. SODIUM/POTASSIUM RATIO IN CERVICAL AND NASAL MUCUS AND THE CORRESPONDING SMEARS DURING NORMAL PREGNANCY

PATIENT NO.	8TH WEEK				12TH WEEK				16TH WEEK				20TH WEEK				24TH WEEK				28TH WEEK				32ND WEEK				36TH WEEK			
	CX*	SR*	NL*	SR*	CX	SR	NL	SR	CX	SR	NL	SR	CX	SR	NL	SR	CX	SR	NL	SR	CX	SR	NL	SR	CX	SR	NL	SR	CX	SR	NL	SR
1	2	+	3	+	5	+	2	+	3.5	–	2	+	2	–	3	+	6	+	4	+	2	+	1.3	+	1.5	+	2	+	2	+	1.5	+
2	2	+	1.5	+	3	+	3	+	3.5	+	3	+	3	+	5	+	7	–	3	+	7	–	5	+	8	+	3	+	4	–	4	+
3	3	+	4	+	4	+	3	+	3	+	4	+	3	+	3	+	4	+	3	+	1	+	5	+	2	+	2	+	2	+	1.5	+
4	5	–	4	+	4	–	4	–	5	+	2.5	+	3	–	2	+	1.5	–	3	+	1.5	–	5	+	2.5	+	4	+	3	–	3	+
5	3	–	2.5	+	3	–	3	+	3.5	–	2.5	+	3	–	4	+	6	+	10	+	4	+	2	+	2	+	5	+	4	+	2	+
6	4	–	2	+	3	–	2	+	4	–	1.5	+	1.3	–	2.5	+	2	–	4	+	4	+	8	+	5	–	3.5	+	3	–	4	+
7	3	–	4	+	5	–	3	–	6	+	4	+	4	–	3.5	+	2.3	–	4	+	1.5	–	3	–	3	–	2.5	+	2	–	2	+
8	2	–	3	–	3	–	2.5	+	3	–	4	+	4	+	3	+	4	–	3	+	9	–	3	+	3	+	4	+	8	+	4	+
9	5	–	4	+	3	–	3	+	0.3	–	0.2	+	10	+	4	+	7	+	4	+	3	–	6	+	3	–	2	+	2	–	2	+
10	4	–	3	+	3	–	3	+	5	–	4	+	1	–	4	+	0.77	–	0.4	+	4.5	–	11	+	1.5	–	1.1	+	2	–	3	–

*Cx, Cervix. Nl, Nasal. Sr, Smear, –, Negative. +, Positive.

treated with a minimum of dilute hydrochloric acid and water, filtered to remove strands, and the filtrate analyzed for sodium and potassium content by flame spectrophotometry.

The nasal mucus from 30 pregnant women was examined. These were between the ages of 16 and 45, and on admission presented the signs and symptoms of late toxemias of pregnancy. Eight of the patients were nulliparas, 4 were multigravidas, para i, and the remainder were multiparas. The majority were beyond the thirty-second week of gestation and only 3 were through the twenty-eighth week of pregnancy. The weight gain in all the patients varied from 7 to 50 pounds in the last 2 weeks. Proteinuria varied from 0 to 1,650 mg. per 24 hours. Blood pressure readings ranged between normal and 220/138 (Table III). Table III also includes the diagnosis on admission and the diagnosis based on admission smears and follow-up during the course of the disease and in the postnatal clinic. These smears were evaluated on the basis of sodium chloride concentration as reflected in the patterns.

Nasal smears were taken on admission, then hourly in severe cases, and twice daily in others. Larger amounts of nasal mucus were collected, when possible, on admission, during treatment and following recovery, by asking the patient to blow her nose into a bottle. Smears were classified on the basis of the presence or absence of arborizations. When arborizations were present a further classification was made according to whether the pattern showed beaded arborizations (unlinked arborizing crystals) or an atypical fern (deficient or incomplete fern arborization).

Oils of different refractive indices were used to identify the presence of Na or K on the smear. A small drop of oil with the same refractive index as that of sodium chloride (1.54) was placed on the dried smear if crystals were present. A thin wire, the size of a 20 gauge needle, was used to transfer the oil. The same process was repeated on duplicate smears with oils which have the refractive index of potassium chloride (1.49). Crystals with the same refractive index as the oil became invisible. Those with a different refractive index remained visible.

Blood samples were also collected from 10 unselected patients (marked with an asterisk on Table III) for the determination of the plasma level of 17, 21, dihydroxy-20-ketosteroids by the method of Silber and Porter.[6]

Results

Initial observations of the nasal mucus of the 5 patients of the preliminary study indicated that the fern phenomenon could be used for the evaluation of the toxemic state. Two of the 3 pre-eclamptic patients showed no salt arborizations in their nasal smears. Twenty-four hours later, although showing evidence of clinical improvement, their nasal smears remained negative for salt arborizations. These 2 patients passed into the convulsive stage 6 and 12 hours later, respectively. This followed a sudden attack of a severe frontal headache in one and blurred vision, in addition, in the other. The convulsions were soon brought under control and spontaneous labor occurred in both with the birth of a premature child in one case and a stillbirth in the other. The third pre-eclamptic patient whose nasal mucus smears exhibited increased arborization (positive fern phenomenon) improved clinically and was delivered without event.

The 2 patients with eclampsia showed negative nasal smears. Following the control of their convulsions spontaneous labor had not begun. The fetuses were still alive. The pregnancy was not terminated in the first case in view of certain irrelevant circumstances. Eight hours later, following the cessation

TABLE II. SODIUM/POTASSIUM RATIO IN NASAL MUCUS AND THE CORRESPONDING NASAL SMEARS IN PRE-ECLAMPSIA, HYPERTENSION, AND RENOVASCULAR DISEASE

PATIENT NO.	AGE	WEIGHT GAIN (POUNDS)	ALBUMIN (MG.)	BLOOD PRESSURE	EDEMA	Na/K ON ADMISSION	SMEAR	Na/K DURING EARLY TREATMENT	SMEAR	Na/K AT RECOVERY	SMEAR	DIAGNOSIS
1	20	46	0	142/80	3+	0.25	Negative	0.14	Atyp. F.*	10	Atyp.+	Pre-eclampsia
2	17	30	100	174/110	3+	0.50	Negative	0.25	Negative	3	Atyp.+	Pre-eclampsia
3	35	40	40	188/108	3+	1.00	Negative	0.33	Atyp. F.	5	Atyp.+	Pre-eclampsia
4	16	30	80	150/108	2+	0.67	Negative	1.40	Negative	2.5	Atyp.+	Pre-eclampsia
5	21	25	120	170/106	2+	0.25	Beaded arborizations	0.50	Negative	3	Atyp.+	Pre-eclampsia
6	16	45	1440	170/130	Generalized	0.4	Negative	1.00	Negative	5	Atyp.+	Pre-eclampsia
7	33	15	20	168/92	2+	1.00	Negative	2.00	Atyp. F.	7	Atyp.+	Pre-eclampsia
8	28	40	200	144/86	3+	3.00	Atyp. F.+	2.00	Atyp. F.	3.10	Atyp. F.+	Hypertension
9	34	50	75	160/98	2+	4.00	Atyp. F.+	2.50	Negative	3.00	Atyp. F.	Hypertension
10	45	35	30	212/110	Generalized	3.00	Atyp. F.+	3.5	Atyp. F.+	3.00	Atyp. F.+	Renovascular disease

*Atyp. F., atypical fern.

TABLE III. DATA ON PATIENTS

PATIENT NO.	AGE	GRAVIDITY	PARITY	WEIGHT GAIN (POUNDS)	EDEMA	ALBUMIN (MG.)	BLOOD PRESSURE	ADMISSION DIAGNOSIS	DIAGNOSIS BASED ON SMEARS AND FOLLOW-UP
1*	20	i	0	46	3+	0	142/80	Pre-eclampsia	Same
2	17	i	0	30	3+	100	174/110	Pre-eclampsia	Same
3	35	i	0		3+	40	188/108	Essential hypertension	Pre-eclampsia
4*	16	i	0	30	2+	89	150/108	Pre-eclampsia	Same
5*	21	i	0	25	2+	120	170/106	Pre-eclampsia	Same
6	16	i	0	45	2+	1440	170/130	Pre-eclampsia	Same
7	33	v	iv	15	2+	20	168/92	Pre-eclampsia	Same
8	28	ii	i	40	3+	200	144/86	Pre-eclampsia	Hypertension
9	34	iii	i	50	2+	75	160/98	Pre-eclampsia	Hypertension
10	45	xvi	xii	35	Generalized	30	212/110	Pre-eclampsia	Chronic renovascular disease
11*	35	iii	i	10	2+	120	220/138	Essential hypertension	Same
12	37	vii	v	50	1+	30	220/130	Chronic renovascular disease	Same
13*	39	ix	vi	35	2+	0	172/108	Pre-eclampsia	Essential hypertension
14*	37	vii	vi	50	1+	0	148/90	Pre-eclampsia	Essential hypertension
15*	30	v	iii	40	3+	0	170/120	Essential hypertension	Essential hypertension
16*	27	iv	iii	70	2+	1650	130/90	Pre-eclampsia	Same
17	33	vii	vi	15	1+	40	190/110	Essential hypertension	Same
18	38	v	iii	35	3+	50	190/104	Pre-eclampsia (diabetic)	Diagnosis uncertain
19	26	vi	v	20	1+	50	200/130	Renovascular disease	Same
20*	27	vi	v	60	1+	85	170/110	Chronic renovascular disease	Same
21*	36	viii	vi	8	1+	350	250/140	Chronic renovascular disease	Same
22	29	ii	i	50	Generalized	5	160/94	Pre-eclampsia	Same
23	22	i	0	23	4+	180	140/90	Pre-eclampsia	Same
24	44	xii	vii	30	1+	5	178/98	Chronic renovascular	Same
25	35	vi	v	30	2+	200	220/110	Chronic renovascular	Same
26	25	iv	iii	21	1+	150	170/100	Pre-eclampsia	Hypertension
27	45	vii	vi	18	2+	2	190/130	Chronic renovascular disease	Same
28	21	i	0	7	3+	130	138/90	Pre-eclampsia	Same
29	20	i	0	20	2+	300	150/90	Pre-eclampsia	Same
30	23	i	0	30	3+	200	155/95	Pre-eclampsia	Same

*Blood samples were collected from these patients.

of the second and last convulsion, the nasal smear showed a few beaded arborizations. Later smears showed qualitative and quantitative improvement in the arborization. Likewise, there was a concomitant progressive improvement in the urinary output, edema, body weight, blood pressure, and proteinuria. Two weeks later the patient was delivered of a living baby weighing 5½ pounds. The second patient who presented similar symptoms was intentionally left with her pregnancy unterminated. She also was delivered of a living baby weighing 5 pounds, 5 ounces.

These observations indicate that the absence of arborization (negative fern phenomenon) is associated with true toxemia of pregnancy.

Table I, a summary of the Na/K ratio in the cervical and nasal mucus of 10 normal pregnant women, is typical of the results obtained in a total of 30 women.

Table II is a similar summary of the Na/K ratios, but from patients with pre-eclampsia, hypertension, and renovascular disease.

Table III lists the essential clinical data obtained for 30 patients upon admission to the hospital with symptoms of toxemia.

By means of the nasal mucus smear these 30 patients could be divided into 3 groups according to the fern pattern produced. Those whose smears showed no evidence of arborization were called Group 1 (9 patients). Group 2 consisted of those showing crystal nuclei and few small beaded arborizations (3 patients). Group 3, those showing an atypical fern pattern, was the largest (12 patients). Six patients were not included in the classification for various reasons (therapy instituted before sampling or other complications).

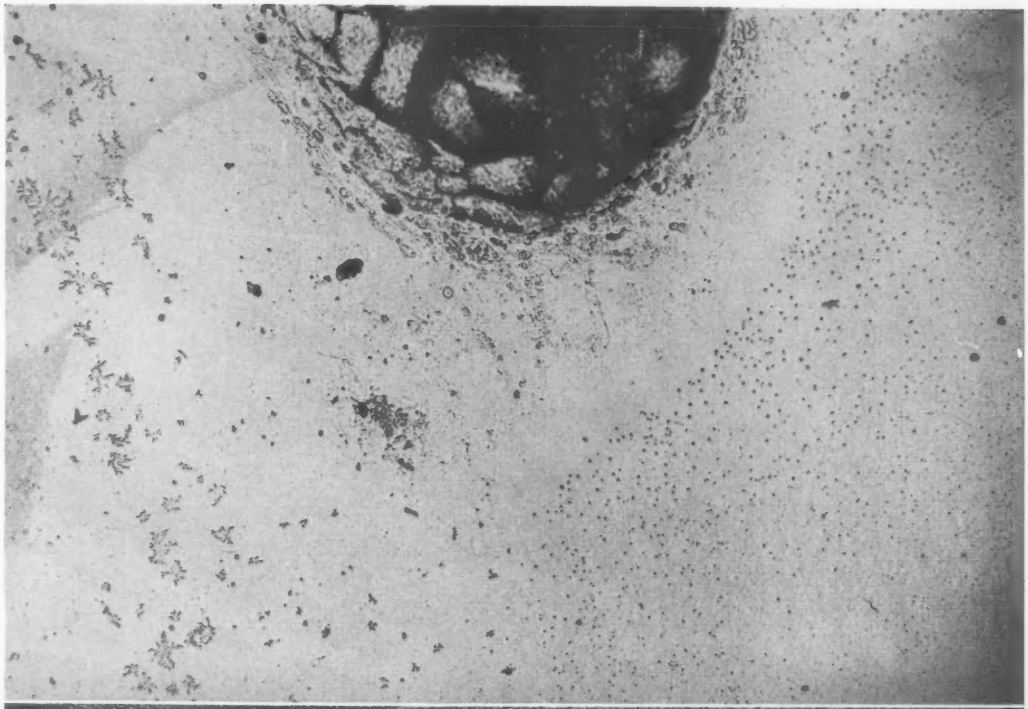
Patients whose nasal smears on admission showed no arborization or showed small light beaded arborizations and only crystal nuclei proved in the follow-up study to have true pre-eclampsia (Groups 1 and 2, Fig. 1). Ten of these patients were nulliparas and 2 were multiparas. The smears of these patients followed a certain pattern during the course of treatment. Depending on the rate of recovery their smears began to show arborizations after about 12 to 48 hours. The pattern soon after became that of an atypical fern. When the crystal pattern of arborizations or atypical ferns showed a preponderance of sodium the patient continued to full recovery. Conversely, when the pattern showed a preponderance of potassium a recurrence of the pre-eclampsia occurred.

Following complete clinical recovery patients were discharged unless they were very close to term. Only one of these patients lost her child. She was an elderly Negro primipara (No. 3, Table III) who was delivered at home. The child died during labor. None of the patients in this group became clinically worse when the nasal smear showed both arborizations and a preponderance of sodium chloride. Nine of the patients went into spontaneous labor presumably at term. The tenth patient had a prolonged desultory labor and therefore had a cesarean section. Labor was induced in the last 2 patients in view of a relapse of the condition clinically; induction was surgical in one and by a Pitocin drip in the other. Their nasal mucus smears showed atypical ferning but with a preponderance of potassium.

Fig. 1.—A nasal mucus smear taken on admission from a patient with pre-eclampsia. Note the few light beaded arborizations on the right and the microcrystals on the left. In the center a poulticelike mass of thick mucoid material and exfoliated epithelium is seen.

Fig. 2.—A nasal mucus smear taken on admission from a nonpre-eclamptic toxemia patient. Note the atypical fern, the symbol of higher salt concentration. This pattern is comparable to that of normal pregnancy. The drop of oil in the center has an index of refraction equal to that of a crystal of KCl (1.49). It is evident that the fern is composed of sodium chloride crystals.

Fig. 1.



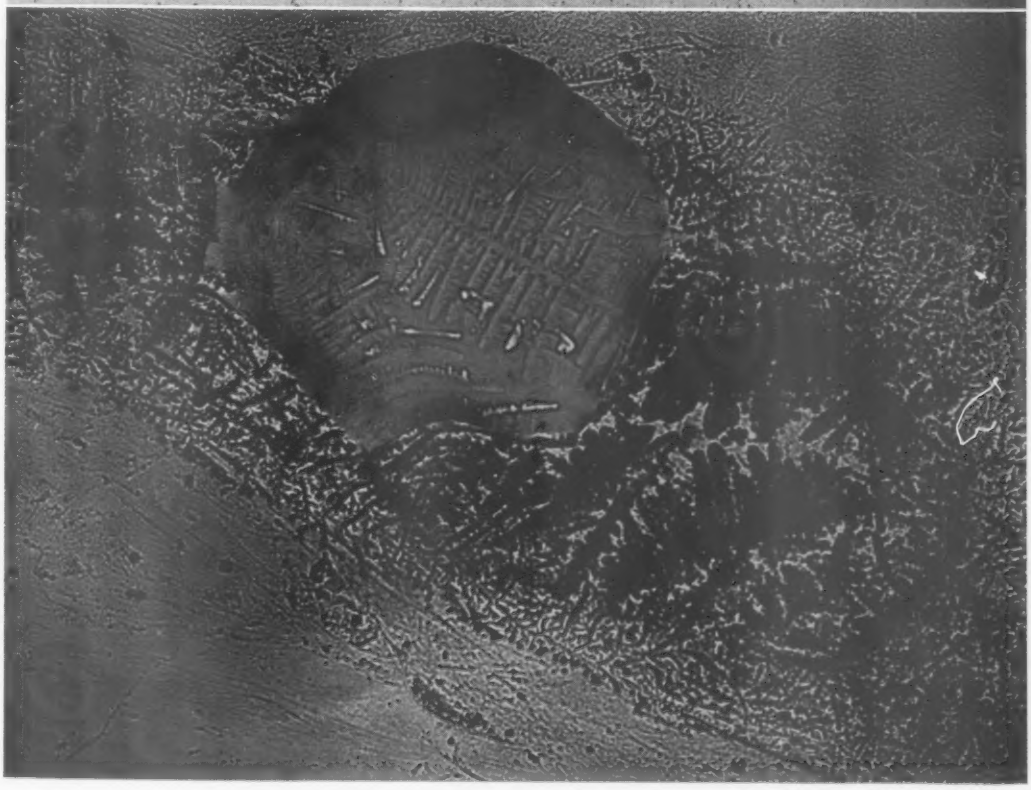


Fig. 2.

Figs. 1 and 2.—*For legends see opposite page.*

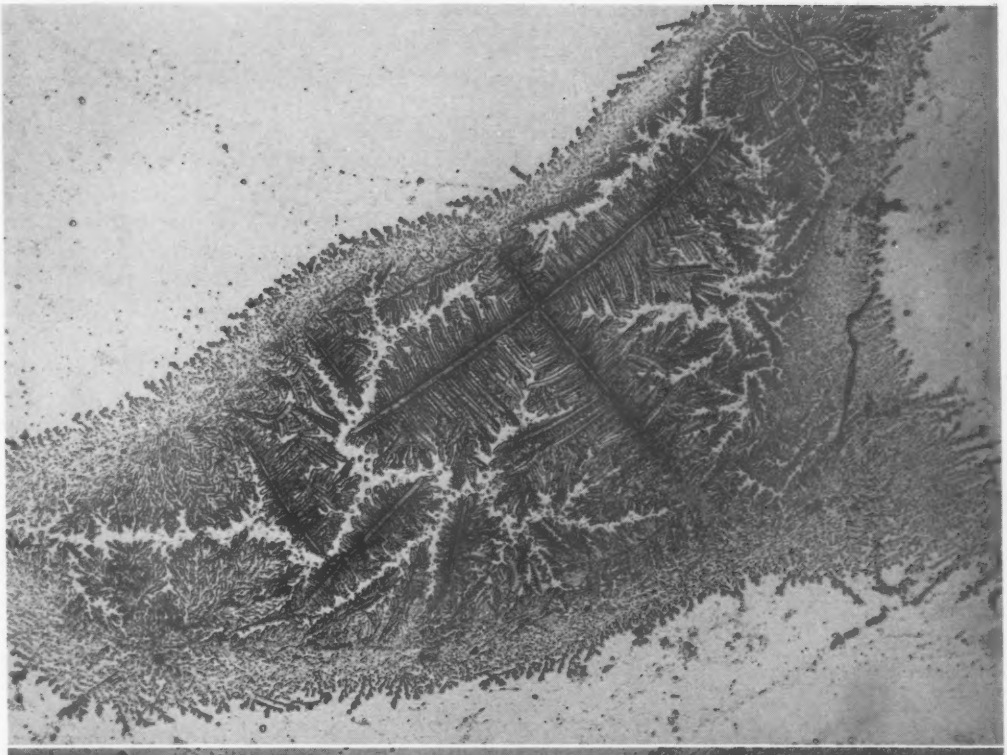
Fig. 3.

Fig. 4.

Fig. 3.—A nasal mucus smear taken from a pre-eclamptic patient during apparent clinical remission. Note the atypical fern pattern. Relapse occurred 2 days later. The drop of oil has an index of refraction equal to that of a crystal of NaCl (1.54). It is evident that the crystals are largely KCl crystals.

Fig. 4.—This photograph is of another area in the same field depicted in Fig. 3. The oil (I.R. 1.49, KCl) test shows that only a small amount of sodium chloride is present.

Fig. 5.



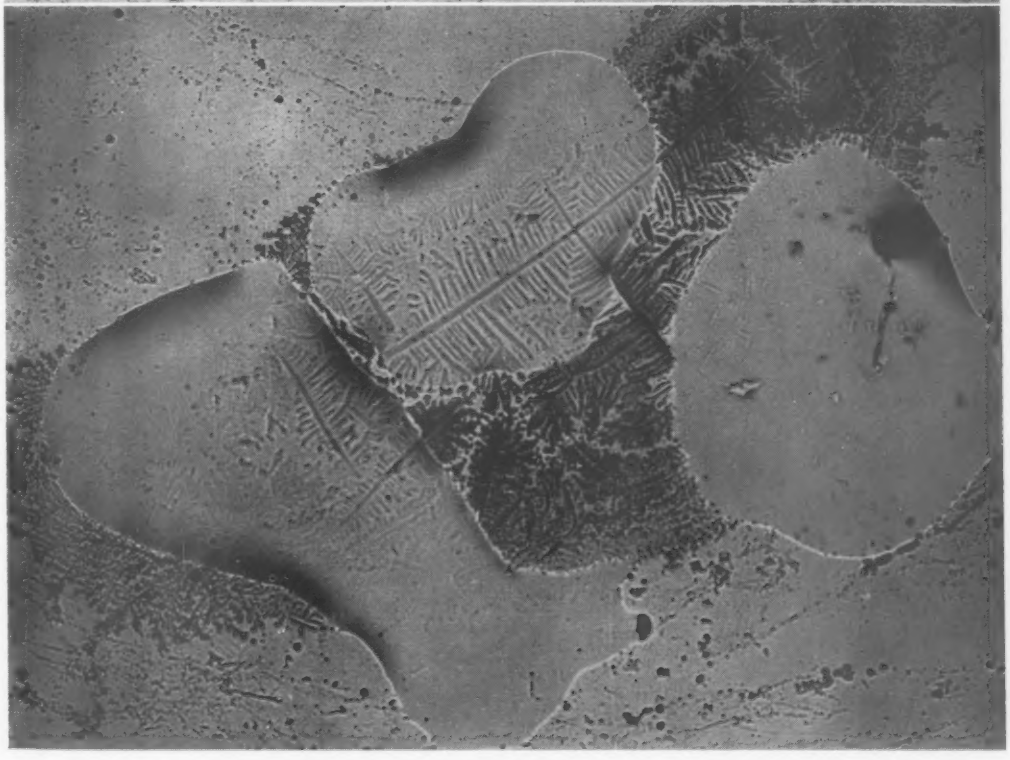


Fig. 6.

Fig. 5.—A nasal mucus smear taken at midcycle from a nonpregnant woman with a normal menstrual cycle. Note the typical fern pattern which is mainly sodium chloride.

Fig. 6.—The same field depicted in Fig. 5 to show the normal marked preponderance of sodium chloride during the phase of maximum electrolyte output. The oil drop on the right (I.R. 1.54 NaCl) indicates the presence of very little KCl, whereas the drops center and left (I.R. 1.49, KCl) show the presence of large amounts of NaCl.

Conversely, the 12 patients whose nasal smears on admission exhibited the atypical fern pattern were shown, in their follow-up study, to have hypertension and/or renovascular disease (Group 3, Fig. 2). In this series all were multiparas. The course of the salt arborization pattern in their nasal smears following therapy was variable. It did not correspond to their clinical condition nor was it useful in predicting the prognosis. The management of these patients, therefore, was based entirely on their clinical course.

The changes in the output of sodium and potassium chlorides were easily detected by using the refractive oils. When pre-eclamptic patients began to show arborizations in their smears during treatment the nature of the crystals could be determined instantaneously and the further course of management could thereby be decided upon (Figs. 3 and 4).

The range of values of the plasma levels of 17, 21, dihydroxy-20-ketosteroids as well as their mean was similar to those in normal pregnancy.

Comment

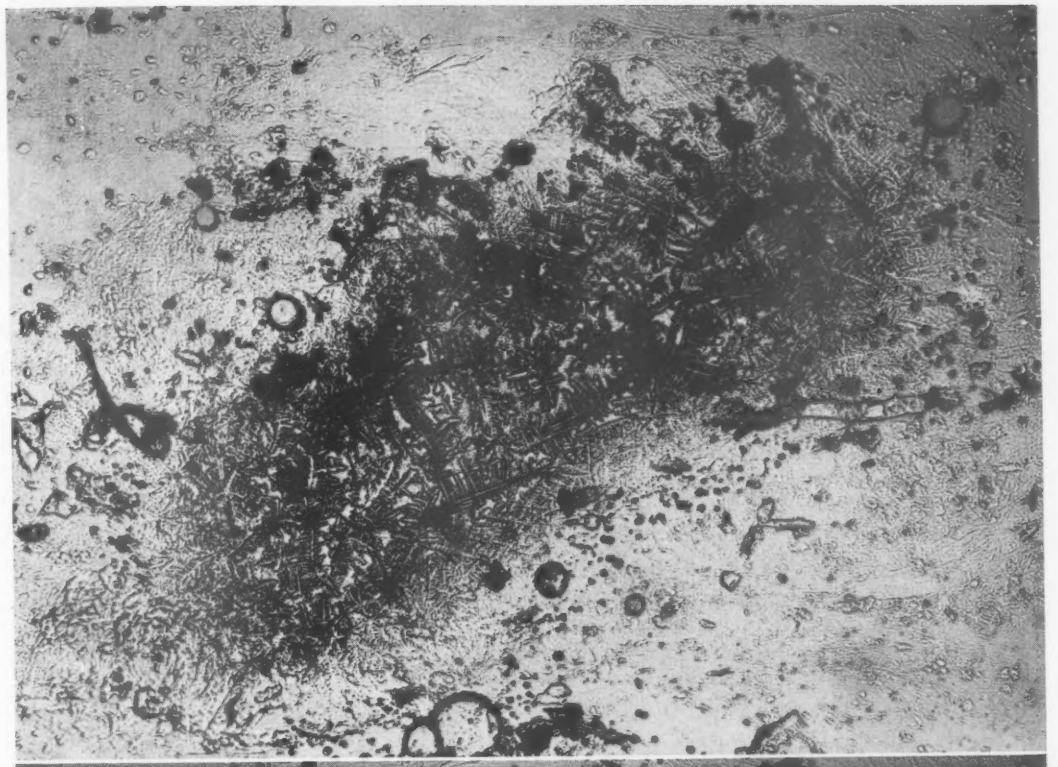
The electrolyte concentration of mucus secretion, like that of other secretions, is influenced by the various hormone levels. Active estrogens, especially estradiol, in small amounts cause water secretion while in large amounts they cause water retention.[7, 8] Water retention is always accompanied by sodium chloride retention and vice versa. Serum estrogens are known to rise to a high level following complete formation of the placenta. Likewise serum progesterone rises steadily but to a much higher level. It is known to be the most important factor in causing premenstrual fluid retention. Further serum levels of the adrenal corticosteroids are now known to undergo certain changes during pregnancy. It has been suggested by Selye[9] that hyperfunction of the maternal adrenal cortex might be the cause of pre-eclampsia. The evidence, to date, for such a hypothesis from measurements of blood and urinary steroid levels is not convincing. For example Venning and Dyrenfurth[10] have reported increased urinary excretion of the mineral corticoid, aldosterone, in toxemia patients as compared with normal pregnant women. In a later study, however, Venning and associates[11] found no such increase. The difference between these two studies may lie in the different techniques employed. In the first study only free aldosterone was measured, whereas in the latter the conjugates were included since acid hydrolysis preceded the extraction procedure. It is thus quite possible that, although the adrenal cortex produced similar amounts of aldosterone in the two groups, the hepatic inactivating function in the toxemic patients was deficient. It would, perhaps, be of value to test this hypothesis by measuring both the free and conjugated aldosterone excretion in the same patients. When a satisfactory method for determining blood aldosterone levels is worked out it may be possible to demonstrate a disproportion in the inactivation rates of aldosterone in normal versus toxemic pregnancies.

There appears to be less evidence for any difference in glucocorticoid metabolism in the toxemias. Our results in 10 unselected toxemia patients were not substantially different from those reported by Robinson and coworkers[12] in normal pregnancy during the last trimester.

Probably much more important is the already established fact of a disturbed adrenal placental interrelationship. Hormone interrelationship is reflected in the nasal mucus smears of the nonpregnant woman, the pregnant woman, and those with toxemia of pregnancy.

The direct effect of this disturbed relationship is the interference with sodium excretion and its storage. Intracellular sodium, however, does not cause as much water retention as extracellular sodium does. Nevertheless,

Fig. 7.



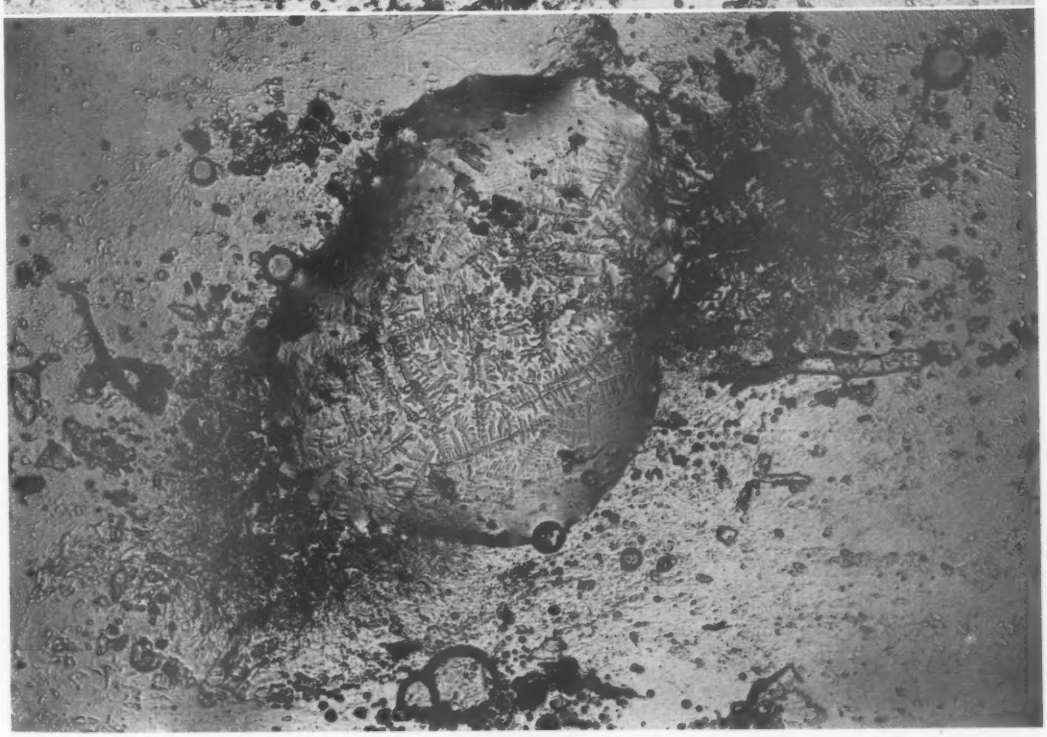


Fig. 8.

Fig. 7.—A nasal mucus smear showing the atypical fern of normal pregnancy.

Fig. 8.—The same field depicted in Fig. 7 but with an oil drop (I.R. 1.49, KCl). The atypical ferns are mainly NaCl crystals.

there is eventually enough water retained to cause rapid weight gain. The displaced potassium is excreted. The kidneys excrete the major part of this potassium but other channels also share this process. The quantities excreted by the nasal mucus, although small in amount, are detectable by the smear procedure described.

The question arises, however, as to the role of this amount of potassium in fern formation. Abou-Shabanah[13] has shown that all salts at certain optimum concentrations produce the typical fern pattern. On the other hand, at other concentrations the patterns are atypical, being incomplete ferns and beaded or unlinked arborizations. The kidneys can excrete sodium to a maximum concentration of 0.8 Gm. or about 0.04 to 0.05 Gm. per cent (1,500-2,000 c.c. urine per 24 hours). It has been previously reported[14] that a smear taken from normal urine shows no arborizations. When the salt concentration was raised by reducing the volume of urine by evaporation the reaction became positive. Potassium which is excreted normally in minute amounts therefore contributes very little to fern formation in the nonpregnant (Figs. 5 and 6) and in normal pregnancy (Figs. 7-11). On the other hand, in true toxemias of pregnancy potassium contributes relatively more to fern formation.

In searching for a simple method of identifying electrolyte variations in body fluids microscopically the senior author adapted the oil refractive index technique to its first clinical usage. This test has formerly been used by mineralogists and analytical chemists. It has the advantage of detecting changes in sodium chloride output at an early date in addition to being a simple and accurate procedure. Changes in sodium chloride excretion were always observed to precede those of potassium chloride excretion. Five of the pre-eclamptic patients, in spite of their clinical improvement and the positive nasal smears, had a relapse. Therefore, the presence of arborizations, in itself, cannot be assumed to indicate clinical remission. It is the amount of sodium chloride and the ratio of sodium to potassium which are the important factors.

The nasal smear is better than the cervical smear in that it shows arborizations in almost all cases of normal pregnancy. The reason for this has been previously explained by Ullery, Livingston, and Abou-Shabanah.[15] Similarly, the nasal smear is better than the urinary smears. In order for the latter smears to be of practical value urine has to be concentrated to a level where the fern phenomenon is induced. The nasal smear, therefore, is the more suitable and is much simpler to obtain in the office as well as in outpatient clinics. If it is necessary to identify salt microcrystals or faint beaded arborizations better, phase microscopy is useful.

On the basis of these observations it cannot be stated whether sodium retention is the cause or an effect of the toxemic state. When sodium chloride excretion becomes sufficient to produce the atypical fern pattern of normal pregnancy in nasal smears, the patient always improves. The fetus also, unless it died earlier, remains alive. Conversely, clinical improvement does not mean that sodium chloride excretion has reached its normal level. The smear pattern may show the beaded form of arborizations. Patients discharged at this stage in our experience were readmitted a few days later with a relapse.

Last, there seems to be a correlation between salt excretion and the condition of the fetus. Since potassium is the normal cation for intracellular function, it is possible that its replacement by sodium will interfere with cell metabolism. When interference is excessive the maternal organism succumbs and the fetus is in danger. On the other hand, the fetal body cells may also be sharing the same process. In any event, additional studies are necessary to avoid unnecessary premature terminations of pregnancy or prematurity.

Fig. 9.

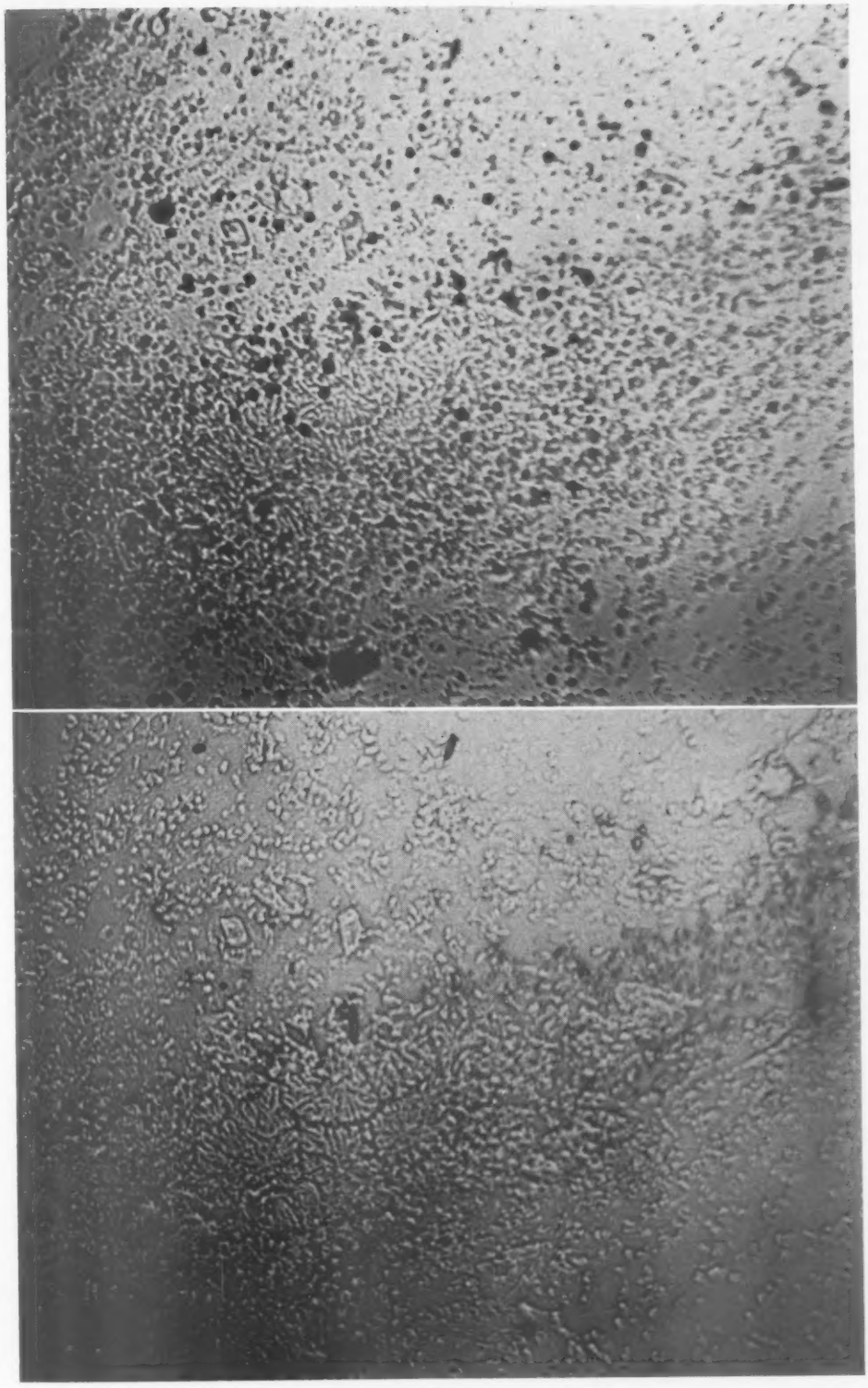


Fig. 10.

Fig. 9.—Cervical smear taken at the thirty-fourth week from a normal pregnant woman. Note at this plane the thick mucoid material and exfoliated epithelium.

Fig. 10.—The same field depicted in Fig. 9 to show an archipelagic pattern of atypical ferning normally present in smears of some patients at a higher plane than that of the organic material.

Unlike pre-eclampsia-eclampsia, hypertensive pregnant patients and pregnant patients with renovascular disease present a different problem. Our findings indicate that these patients are able to concentrate sodium chloride to the same degree as normal patients. The nose is an excretory channel and, like the kidney, seems to exercise the ability to concentrate sodium chloride in nonpre-eclamptic toxemic patients. The pattern noted in the nasal smears of all the patients in Group 3 was similar to the pattern commonly observed in normal pregnancy. Renal function studies, urine examination, and the follow-up studies of these patients established the diagnosis.

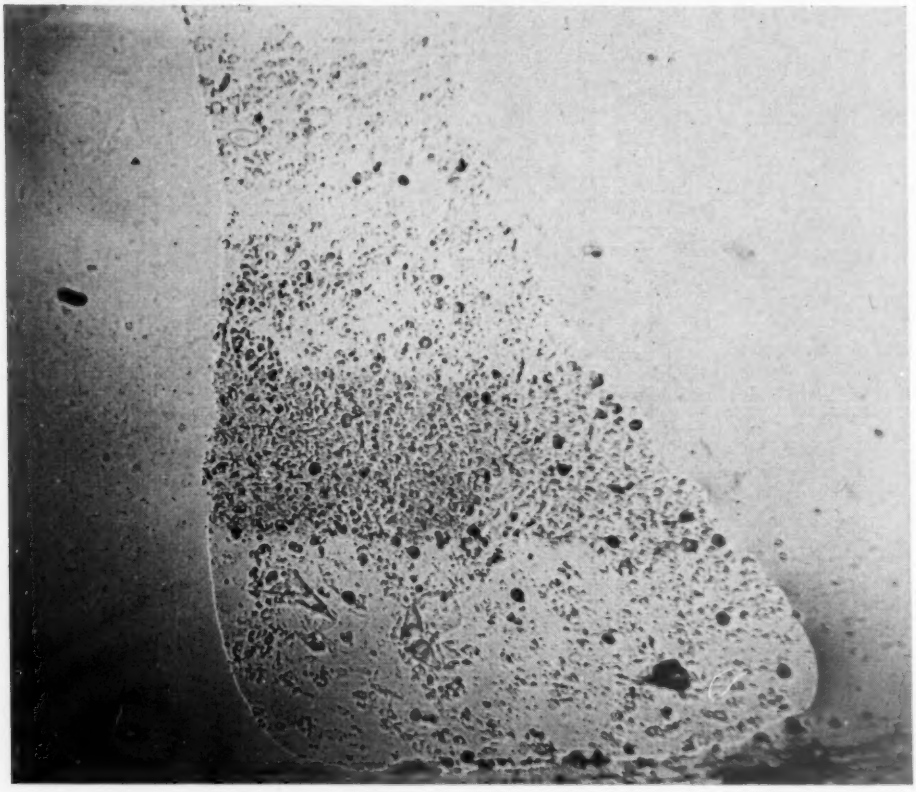


Fig. 11.—This photograph is the same field depicted in Figs. 9 and 10 and illustrates atypical ferns. That NaCl is the principal salt of mucus smears in normal pregnancy is evident by observation of the oil drop on the right (I.R. 1.54, NaCl) and the oil drop on the left (I.R. 1.49, KCl).

There was no substantial difference between the Na/K ratio in these patients and the ratio in normal pregnancy. This is also very evident in the nasal smears treated with refractive oils. Following the institution of treatment, however, the behavior of the salt pattern in nasal smears obtained from this group of patients became unpredictable. In some the smears remained strongly positive, while in others it alternated. The prognosis and management of such patients, therefore, cannot be based, at present, on smears of their nasal mucus.

On the other hand, at the onset of the disease the difference between the smears of the nasal mucus obtained from patients with pre-eclampsia-eclampsia and hypertensive-renovascular disease is so marked that it merits attention.

Conclusions

1. The absence of arborization (negative fern phenomenon) in a smear of nasal mucus is associated with pre-eclampsia-eclampsia.

2. The sodium/potassium ratio of the nasal mucus of normal pregnant women and of pregnant women with hypertension and/or renovascular disease is greater than one, whereas, in pre-eclampsia-eclampsia it is reversed.

3. The use of index of refraction oils on smears of nasal mucus will enable the physician to detect pre-eclampsia by a simple office test.

4. This test also guides the physician in the management of and prognosis for both the mother and the fetus during the course of the disease.

The senior author wishes to acknowledge the service offered to him by Dr. A. Timnick of the Chemistry Department of Michigan State University, East Lansing. His cooperation in searching for a spot test for identifying crystals proved invaluable.

We also wish to offer our gratitude and deep appreciation to Dr. Wilfred R. Foster, professor and chairman of the Department of Mineralogy, Ohio State University, for his cooperation and invaluable help.

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EVALUATION OF A DIURETIC SUBSTANCE IN THE MANAGEMENT OF MILD PRE-ECLAMPSIA

A Report of 47 Clinical Trials

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THE xanthines have long been known to have a considerable diuretic action with an absence of toxic effects. Large doses have hemodynamic actions which cause increased cardiac output, renal blood flow, and glomerular filtration rate, in addition to depressing the renal tubular reabsorptive transportation of electrolytes.[1]

Of the xanthines (caffeine, theobromine, and theophylline), theophylline has been much used clinically for its diuretic properties In recent years a preparation, 2-amino-2-methyl-1-propanol-8-bromotheophyllinate combined with pyrilamine maleate,* has had widespread use in the treatment of premenstrual edema with appreciable success Bickers[2, 3] was the first to report the clinical effectiveness of this compound and demonstrated that it would effectively block the known antidiuretic effect of experimentally injected vasopressin. Berman and Greenblatt[4] and Greenblatt[5] experimentally showed that the substance removed sodium, potassium, and chloride ions, as well as water. Since Greene and Dalton,[6] Dalton,[7] Helig,[8] and Thomas[9] have noted that premenstrual edema and the edemas of pregnancy have signs and symptoms that indicate the involvement of identical etiological factors, James and Johnson[10] used the 2-amino-2-methyl-1-propanol-8-bromotheophyllinate combined with pyrilamine maleate in treating the edemas of pregnancy.

They did not alter the patients' dietary habits or restrict fluid intake, and found the drug to be 90 per cent effective if given in dosages twice that used in treating premenstrual edema. They concluded that the compound is not effective in treating the true toxemias of pregnancy, since the 10 per cent failures were all eventually classified as such and showed no response to standard toxemia therapy.

Methods

This study was done as a follow-up of the work of James and Johnson.[10] As the diuretic properties of theophylline preparations are well known, it was felt that the 2-amino-2-methyl-1-propanol-8-bromotheophyllinate without the

*Marketed as neo-Bromth by Brayten Pharmaceutical Company, Chattanooga, Tenn.

pyrilamine maleate would get equally good results. And since James and Johnson noted that larger dosages were required than those used in treating premenstrual edema, 800 to 1,600 mg. of the preparation* was given in each 24 hour period. Patients were selected on the basis of the following criteria: (1) 2 pounds or more weight gain per week; (2) the presence of edema; (3) normal or slightly elevated blood pressure; (4) no more than a trace (30 mg. per cent) to a "one plus" (100 mg. per cent) albuminuria; and (5) past 22 weeks' gestation. Thus, the patients would be classified as having mild pre-eclampsia according to Dieckmann's[11] criteria. Because of the findings of James and Johnson, none with severe pre-eclampsia were included.

Special charts were kept on all patients, giving the age, parity, gravidity, gestation, usual weight, history of previous pregnancies, urine albumin (before and after treatment on outpatients, daily on inpatients), urinary sodium, chloride, potassium, creatinine (before treatment and on the fifth or seventh day of treatment of inpatients), blood pressure (before, during, and after treatment), daily intake and output of fluids (on inpatients), edema before and after treatment, indication of nausea, vomiting, changes in vision, changes in fetal movement, headache, and miscellaneous side effects.

Thirty-eight patients were included in the study, which was repeated on 9 of these, thus making a total of 47 clinical trials.

Sixteen of the subjects were inpatients. Intake and output of fluids was recorded for each 24 hour period in 10 of these patients. The patients were ambulatory and food and fluid intake were not altered while they were on the study. Urinary sodium, chloride, and potassium output was recorded on a 24 hour specimen prior to institution of therapy and again on the fifth or seventh day of therapy. Urinary creatinine determinations were made prior to institution of therapy and on the fifth or seventh day of therapy, also, to rule out any kidney disease. The electrolyte content of the urine (sodium, chloride, potassium) was assayed on both a 24 hour and per liter basis.

Thirty-one of the subjects were followed as outpatients. No effort was made to limit fluid or food intake and no medication other than 2-amino-2-methyl-1-propanol-8-bromotheophyllinate was used. These patients were given 5 to 7 days' diuretic therapy. Electrolyte studies were not done as it was felt that the determinations made on the 10 inpatients gave a clear indication of the effect of the compound on electrolyte output. The patients were not required to change their habitual mode of living in any way.

TABLE I. THIRTY-EIGHT TRIALS: 35 RESPONSES, 3 FAILURES

DOSE	NO. OF PATIENTS	WEIGHT CHANGE*	EDEMA CHANGE*
200 mg. q.i.d.	29	–	–
200 mg. q.i.d.	3	0	–
200 mg. q.i.d.	3	+	–
200 mg. q.i.d.	1	0	0
200 mg. q.i.d.	2	+	0
Total	38		

*–, Decrease; 0, no change; +, increase.

Results

Twenty-nine of the 38 patients included in the study lost weight and edema after 5 to 7 days of Predema therapy. Three of the subjects did not lose weight but ceased to gain and were less edematous. Three of the patients gained weight, but at a less rapid rate and were less edematous. One

*Supplied in 200 mg. tablets as Predema by the Brayten Pharmaceutical Co., Chattanooga, Tenn.

patient did not lose edema but, also, did not change in weight. Two patients gained weight and retained edema on therapy (Table I). These 38 patients received the medication at the rate of 200 mg. four times a day (800 mg. daily).

The dosage was increased to 400 mg. four times a day (1,600 mg. daily) in the 9 patients without weight loss (a total of 47 clinical trials). The 3 patients who had no weight change and the 3 patients who gained weight, while losing edema, then lost edema and weight on the increased dosage. The patient who lost no edema and no weight again failed to respond. Of the 2 patients who not only retained edema but gained weight, one patient continued to gain weight and edema and had a progressive rise in blood pressure. She failed to respond to other forms of therapy (including a carbonic anhydase inhibiting diuretic) and must be classified as having severe pre-eclampsia. The other one did not lose weight and did not lose edema (Table II). Hence, only 2 of those with mild pre-eclampsia failed to respond.

TABLE II. NINE TRIALS: 6 RESPONSES, 3 FAILURES

DOSE	NO. OF PATIENTS	PREVIOUS TRIAL	WEIGHT CHANGE*	EDEMA CHANGE*
400 mg. q.i.d.	3	Weight gain	–	–
400 mg. q.i.d.	3	No change	–	–
400 mg. q.i.d.	1	Weight gain	0	0
400 mg. q.i.d.	1	No change	0	0
400 mg. q.i.d.	1	Weight gain	+	0
Total	9			

*–, Decrease; 0, no change; +, increase.

One patient with a diagnosis of hypertensive cardiovascular disease prior to pregnancy was included because of superimposed mild pre-eclampsia, as her blood pressure was adequately controlled by reserpine drugs. She continued a too rapid weight gain and developed edema, despite reserpine therapy. This patient responded well to the diuretic therapy after 5 days' medication.

Of the 10 patients upon whom electrolyte determinations were made, all excreted urinary electrolytes in greater amounts when sodium, chloride, and potassium were measured on a 24 hour or per liter basis. Five of the 10 patients, although they either gained weight or did not lose weight, did lose edema, as well as electrolytes. One patient lost neither weight nor edema but still excreted more electrolytes while on therapy (Table III). One of the patients who responded well was anemic and required transfusion, but later, with recurrence of symptoms (after the anemia was controlled) again responded to therapy.

None of the 47 patients developed any toxic effects from the drug.

TABLE III

NO. OF PATIENTS	WEIGHT CHANGE*	EDEMA CHANGE*	ELECTROLYTE EXCRETION
4	–	–	+
3	0	–	+
2	+	–	+
1	0	0	+
Total 10			

*–, Decrease; 0, no change; +, increase.

Comment

Since 35 patients lost weight and edema, 3 ceased to gain weight and showed a decrease in edema, and 3 gained weight moderately but lost edema, it is evident that 41 out of 47 patients showed response to therapy.

The loss of urinary sodium, chloride, and potassium by the 10 patients on whom assays were made indicates that the 2-amino-2-methyl-1-propanol-8-bromotheophyllinate without the added pyrilamine maleate is effective in causing diuresis of electrolytes. The limitations of this study prevent any conclusions concerning the blockage of the antidiuretic effect of vasopressin.[2, 3]

The use of doses up to 1,600 mg. per 24 hour period without any toxic effects is evidence of the safety of the compound.

The large doses required bear out the findings of James and Johnson[10] that the edemas of pregnancy require a greater dosage for a response than does premenstrual edema.

The fact that approximately 87 per cent of the subjects showed some response indicates that the addition of pyrilamine maleate apparently does not enhance the diuretic effect of the preparation when used to treat the edemas of pregnancy.

The study of James and Johnson and the results of this series are evidence that 2-amino-2-methyl-1-propanol-8-bromotheophyllinate is a useful addition to the armamentarium to preclude pre-eclampsia, especially since the loss of weight and edema can be effected without a strict change in dietary habits and a restriction of fluid intake which are so difficult to enforce in the pregnant outpatient.

The compound is most helpful in managing mild pre-eclampsia which is not severe enough to require hospitalization, but yet is one of the more vexing problems in daily obstetrical practice.

Summary

1. 2-Amino-2-methyl-1-propanol-8-bromotheophyllinate is effective in controlling the edemas of pregnancy without restriction of the habitual fluid and food intake of patients, if given in large doses (800 to 1,600 mg. per 24 hours) and limited to the pregnant patient with mild pre-eclampsia.

2. The preparation causes diuresis of sodium, chloride, and potassium ions and has no apparent side effects in the doses given.

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PSYCHOPHYSIOLOGIC ASPECTS OF THE TOXEMIAS OF PREGNANCY*

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OF ALL the phases of obstetrical and gynecological dysfunctions, the student of psychosomatic medicine has made the least impression in the sphere of the toxemias of pregnancy, more especially pre-eclampsia and eclampsia. Perhaps the reason for this failure is related to the fact that though the very nature and etiology of pre-eclampsia are still unsolved and little understood, it has always been regarded as a purely somatic disorder with definite organopathological changes. Little attention has been paid to adaptational and psychosomatic aspects of this problem which frequently confront the obstetrician but apparently have scarcely been related by him to this condition.

Thus, historically, there has been a long-standing continuous search for some "toxin" or noxious substance capable of causing and accounting for the various somatic changes which are characteristically manifest in the liver, kidney, brain, and other organs. These theories and hypotheses have varied from the effects of meteorological changes and Selheim's theory of mammary toxins to the present-day concept of uterine ischemia.

Although the clinician is well oriented to the relationship of hypertension, nephrosclerosis, cardiovascular and gastrointestinal diseases to abnormal adaptive reactions to stress,[1] nonetheless the similarity of toxemia of pregnancy to other diseases of known psychosomatic pathogenesis has been ignored.

Pathogenesis

Any attempt to explain the mechanism of pre-eclamptic toxemia must of necessity explain two physiochemical disturbances, namely, (1) salt and water retention and (2) arteriolar spasm. These disturbances are generally recognized and accepted as the basic changes found in toxemia of pregnancy which account for the triad of hypertension, edema, and albuminuria. However, although we have acquired a more complete understanding of the physiological and pathological changes involved in this syndrome, we have failed to determine by what mechanism these changes are initiated and mediated. Recent investigations have demonstrated the important roles of the adrenals

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and the adrenal corticosteroids in the mechanism of salt and fluid retention, as well as the possible influence of the autonomic nervous system, mediated through the hypothalamic-pituitary-adrenal system in the production of hypertensive states.

Role of Adrenal Cortical Hormones.—It is recognized that the adrenal cortical steroids are definitely related to salt metabolism.[2] Tobian[3] demonstrated that pregnant women with marked edema excreted 46 per cent more corticosteroids than pregnant women with little or no edema. Excessive activity of the adrenal cortex releasing large amounts of adrenal cortical hormones may be an essential feature of toxemia of pregnancy which results in derangements of salt metabolism leading to albuminuria, edema, and hypertension.[4] In fact, Garrett[5] concluded that "steroid hormones from the adrenal cortex come closest to matching the long held concept of a circulating toxin as the cause of eclampsia."

Role of Pressor Substances.—In view of the significance of arteriolar spasm and hypertension, pressor substances may be implicated in the pre-eclampsia syndrome. Hofbauer[6, 7] has suggested several mechanisms for the production of pressor substances, i.e., (1) norepinephrine produced by marked hypertrophy of the sympathetic ganglia in the pelvis (Frankenhäuser's plexus) and (2) vasopressin in the form of increased epinephrine and norepinephrine secretions of the adrenal cortex. He believes that an overactive hypothalamic-pituitary-adrenal system may exercise a dominant influence in the excessive production of hormones.

The Role of Stress.—The concept of overactivity of the pituitary-adrenal system with excessive secretion of adrenal cortical hormones and/or vasopressin is an approach to the problem of toxemia of pregnancy which has been inadequately explored. The role of the hypothalamus similarly needs investigation, for the hypothalamus may serve as the initiator of this mechanism via psychosomatic stress disturbances. It has long been recognized in pure hypertensive states, whether associated with pregnancy or not, that a neurogenic component may be the etiological factor.[8] The labile blood pressure during normal pregnancy, and especially in early pre-eclampsia, offers ample evidence that the vasoconstrictor fibers of the autonomic nervous system are abnormally active. Holland and Bourne[9] stressed that "emotional tranquillity and complete physical rest is the ideal at which to aim" in the control of pre-eclampsia.

Certainly under emotional stress it is a recognized and accepted fact that hormone output may increase. Selye,[10] in elaborating his "alarm-stress" reaction, has demonstrated the responsiveness of the adrenal cortex to emotional stimuli. Experimentally and therapeutically we have noted innumerable instances of edema and hypertension, with sodium and water retention, similar to pre-eclampsia, induced by the administration of desoxycorticosteroids.

Physiological disturbances akin to pre-eclampsia may result from emotional tensions mediated by the autonomic nervous system. When the central nervous system and cerebral cortex are directly affected, hysterical tremors, epileptiform phenomena, etc., may result. There is a mass of clinical evidence

to support the concept of biological responses mediated through the hypothalamus, transmitted to and integrated by the cortex which is concerned with behavior and conditioning. If tensions accumulate and are not relieved by normal pathways of thought and behavior, then these tensions may stimulate the autonomic nervous system and in this manner result in psychosomatic symptoms. Alexander[11] has shown that aggressive emotional impulses tend to affect the autonomic nervous system as in cases of essential hypertension. Hofbauer,[12] Hoffmann and Anselmino[13] and numerous others, at one time implicated the posterior pituitary antidiuretic hormone (ADS). Verney[14] stated that ADS is released in the living animal under emotional stress. This conceivably then might be an important psychosomatic factor in the development of toxemia. However ADS was never proved to be present in significant amounts in toxemia of pregnancy.

The Pre-eclamptic Patient

These neuroendocrine and neurophysiological principles which we have elaborated unfortunately have not had practical application in the evaluation of the pre-eclamptic patient. Our approach to the problem has been purely somatic. For some time we have been struck by the high incidence of pre-eclampsia in young primiparas, and have often wondered what factors, other than poor nutrition and inadequate prenatal care, were involved in the development of toxemia in this group of young, otherwise healthy women.

In the socioeconomic group which has been the chief source of our observations, we find that the young girls between the ages of 13 and 25 are usually the most well developed physically and nutritionally, being in the prime of life, as compared to their older sisters, 25 to 45 years of age, who are worn with the burdens of many children as well as the wear and tear of the passing years. Why then, under the same conditions of poor and inadequate diet and often inadequate prenatal care, should the incidence of pre-eclamptic toxemia be so much greater in the younger group which physically should be able to withstand these deficiencies much better than the older group of patients? There seem to be other factors involved, for the differences in diet and nutritional intake are not that marked. In fact, there are frequently greater nutritional deficiencies noted in the older age groups, associated with self-deprivation and greater economic hardships in the cases of women with large numbers of children to feed. This brief survey, submitted in the nature of a preliminary report, will reveal certain significant and interesting highlights which may point the way to a better psychiatric investigation of this problem.

Material for Study

The material for this study consisted of women who were predominantly Puerto Rican in origin (approximately 90 per cent), the remainder being American Negroes. The socioeconomic level of these patients is such that complete cooperation in prenatal management is rarely achieved because of such factors as low intelligence levels, language and tradition barriers, and economic want.

Survey of Cases

A recent survey of 1,176 consecutive deliveries at the New York Medical College-Metropolitan Hospital Medical Center disclosed the following data.

In this series, there were 51 cases of severe toxemia of pregnancy. Using the criteria of elevated blood pressure of 160/100 or greater, and 3 to 4 plus albuminuria and/or 3 to 4 plus edema, all mild or questionable cases were eliminated from this preliminary report (Table I). Thirty-four cases were pre-eclampsia-eclampsia and 17 cases were chronic hypertensive vascular disease with or without superimposed pre-eclampsia. It is interesting to note that 20 of the 34 patients with pre-eclampsia-eclampsia were primigravidas, that 10 had borne but one child, and only 4 had two or more previous children (Table II). Twenty-six out of 34 patients with pre-eclampsia-eclampsia were under 25 years of age. Of the 17 patients with chronic hypertensive vascular disease, only 2 were primigravidas, whereas 15 had borne from two to eleven children. It is of interest also that in this series of 1,176 consecutive deliveries, there were 10 primigravidas between 14 and 19 years of age with a severe pre-eclampsia-eclampsia syndrome and half of this group were unwed mothers (Table III). It has been our observation that the young teen-age, usually unwed girl, is most apt to manifest the more severe types of pre-eclampsia, often fulminating in type.

TABLE I. INCIDENCE OF TOXEMIA ACCORDING TO AGE

AGE	PRE-ECLAMPSIA	CHRONIC HYPERTENSIVE VASCULAR DISEASE
10-15	3	0
15-19	7	0
20-25	16	0
26-30	3	4
31-35	1	4
36-40	4	5
41 plus	0	4
Total	34	17

TABLE II. INCIDENCE OF TOXEMIA ACCORDING TO PARITY

PARITY	PRE-ECLAMPSIA	CHRONIC HYPERTENSIVE VASCULAR DISEASE
0	20	2
i	10	0
ii	1	3
iii	1	3
iv	1	3
v	1	2
vi plus	0	4
Total	34	17

TABLE III. RELATIONSHIP OF AGE AND MARITAL STATUS IN TEN TEEN-AGE PRIMIGRAVIDAS

AGE	MARITAL STATUS	PRE-ECLAMPSIA-ECLAMPSIA
14	S	E
14	S	P
15	S	P
16	M	P
17	M	P
17	M	E
18	S	P
18	S	P
19	M	P
19	M	P

Comments

It is significant in evaluating the psychological influences in the development of pre-eclampsia, that primiparity and youth play such an outstanding role. It seems strange that this young group, in the flower of youth, should be subject to such extreme and often fatal physiological disturbances, whereas, with the passage of years and the acquisition of infirmities often associated with age, there is a greater resistance to these physical changes. It is estimated that more than 70 per cent of all cases of pre-eclampsia occur in primigravidas. Marchetti and Menaker[15] similarly noted the extremely high incidence of antepartum complications in a group of 634 young mothers between the ages of 12 and 16 years. Toxemia of pregnancy was the most frequent (60 per cent) and most important complication, occurring in 20 per cent of this group. The younger the patient, the higher was the incidence of toxemia. The incidence of primiparity was 93.7 per cent.

The marital status of this young group similarly serves as food for thought. In our group half of the teen-age mothers were unwed. In a European survey,[16] 10.9 per cent of all births reported were illegitimate and 21.3 per cent of all cases of eclampsia occurred in unmarried mothers. The ratio of eclampsia in unmarried mothers was 3.38 per cent per thousand and in married mothers 1.53 per thousand, eclampsia therefore being twice as frequent in unwed mothers.

A 14-year-old unwed child must view the traumatic development of her pregnancy with confusion, fear, and dread born of ignorance and guilt. In 1946, Selye[17] postulated that the general adaptation syndrome is the "sum of all non-specific, systemic reactions of the body which ensue upon long continued exposure to stress." He includes eclampsia in that group of syndromes which he speaks of as "diseases of adaptation." Hypertension, albuminuria, edema, and arteriolar spasm are signs of damage due to abnormal or excessive adaptive reactions to our environment. It is generally accepted that the theory of chronic stress may be mediated not alone through the liberation of some toxic metabolite, but also by direct hypothalamic stimulation of the anterior lobe of the pituitary with consequent discharge of adrenotropic hormones. This in turn stimulates the adrenal cortex to produce an excess of corticoid hormones. Selye and associates[18] stated that experimental observations are compatible with the view that during the general adaptation syndrome certain hormones of the anterior pituitary and adrenal cortex are produced in excessive amounts in order to increase resistance. "This defensive endocrine response is valuable in as much as it facilitates adaptation to stress. but the resulting endogenous hormone overdosage may become the cause of certain cardiovascular and renal diseases." Adaptation to our environment is one of the most important physiological reactions in life. Pregnancy is certainly a major stress felt at all levels; it is a continued stress of measurable duration. The reaction to this continued and prolonged stress is occasionally an "exhaustion stage" syndrome which may manifest itself in three nonspecific abnormal physiological responses to stress, i.e., hypertension, albuminuria and edema.

The effects of environmental stress have been uniquely demonstrated by a study of the incidence of toxemia in aboriginal groups.[19, 20, 21] Bell and Wilk[22] reported that toxemia among native Fijians is extremely rare. These people lead a communal village life, full of laughter and play and without tensions. On the other hand, in an expatriate group of Indians, emigrated to the Fiji Islands many generations back, living uder extreme tensions and psychological stress, the incidence of toxemia was quite high. It is also of

interest to note that the incidence of toxemia of pregnancy is high among schizophrenic patients, particularly in the primiparous group and especially before the first psychotic episode. Wiedorn[23] in his report defined toxemia of pregnancy as a "psychotic equivalent on a physiologic level of response."

It is difficult to ignore the possible relationship in terms of environmental stress of the three factors of youth, primiparity, and unwed status. These factors demonstrate the potential role of emotional tensions, mental anxiety, shame and guilt, fear and apprehension in the development of a neuroendocrine stress mechanism resulting in the development of pre-eclampsia. The teen-age primipara, often unwed, sustains traumatic pressures. It is significant that this pattern of emotional tensions and stress does not affect older women to the same degree (Table I and Table II). The woman who has experienced childbirth in the past is not consumed with the same degree of fear and tension. Bearing her third, fourth, or fifth child out of wedlock, she is less overwhelmed with shame and anxiety than the immature girl with her first pregnancy. With age comes maturity, and a better isolation from social sanctions. Consequently the multigravid woman, no longer youthful, has less emotional stress tending to the development of pre-eclampsia. A closer evaluation of these psychosomatic disorders is needed to determine the extent of the influence of emotional tensions in producing or aggravating a toxemia state. A better understanding of this relationship may lead to better control, and perhaps prevention, of the toxemias of pregnancy.

Summary

1. The pathogenesis of the physiochemical disturbances in pre-eclampsia-eclampsia has been reviewed.

2. Neuroendocrine and neurophysiological factors are postulated as playing a potential role in the development of pre-eclampsia-eclampsia.

3. A preliminary report of 51 cases of toxemia of pregnancy is presented to illustrate the relationship of youth, primiparity, and unwed status to a general adaptation stress mechanism. This may potentially lead to a disturbance of the hypothalamic-pituitary-adrenal axis, resulting in imbalance or excess of adrenal corticosteroids and/or a direct excitation or stimulation of the autonomic (pressor) nervous system, similarly mediated via a hypothalamic-pituitary-adrenal axis.

4. This hypothesis is supported by other clinical studies and observations and merits closer investigation and evaluation.

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PREGNANCY ASSOCIATED WITH THROMBOCYTOPENIC PURPURA AND ECLAMPSIA

Report of a Case

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THE complication of pregnancy by attacks of idiopathic thrombocytopenic purpura (I.T.P.) has been reported in 51 women.[1, 2, 3] There has apparently been no report of the association of toxemia of pregnancy and I.T.P., however. In the following case the onset of I.T.P. occurred during the patient's first pregnancy. The hemorrhagic diathesis improved under treatment with prednisone but was markedly exacerbated during an attack of severe pre-eclampsia progressing to frank eclampsia.

The accepted criteria for the diagnosis of I.T.P. include a history of easy bruising or hemorrhage or both, decreased platelet count, prolonged bleeding time, poor clot retraction, and increased capillary fragility. Pregnancy in patients suffering from I.T.P. involves a definite risk to both mother and infant, with 2.1 per cent maternal mortality and 15.1 per cent fetal mortality, despite the use of adrenocortical therapy.

An 18-year-old woman, married for one year, complained of nasal and gingival bleeding for the first time at the end of the fifth month of her first pregnancy. As the tourniquet test was positive, indicating increased capillary fragility, she was immediately admitted for further investigation. There was no history of a bleeding tendency or blood diseases in her family. The patient had never suffered previously from excessive bleeding or easy bruising. The menarche occurred at the age of 12 with regular menses every 30 days, lasting 3 to 4 days with moderate flow. At the end of the third month of her pregnancy she had slight vaginal bleeding lasting for 2 days which ceased after some days of bed rest. The temperature was 36.8° C. and the blood pressure 100/95. There were no bruises or ecchymoses. The heart and lungs were normal and neither the spleen nor liver was palpable.

Laboratory studies showed the following: The urine analysis was negative. There was a normochromic anemia with 7.9 Gm. per cent hemoglobin and 2.7 million erythrocytes. The blood uric acid was 3.2 mg. per cent. The diagnosis of I.T.P. was established by the finding that the platelets were reduced to 20,000, the bleeding time prolonged to more than 12 minutes, and that clot retraction did not begin until after 4 hours. The capillary fragility was again found to be increased.

Treatment was begun with 30 mg. of prednisone (Meticorten) daily. By the end of the first week, some improvement had occurred. The bleeding from the nose and gums ceased, the platelet count increased to 40,000, the bleeding time ranged between 6 and

12 minutes, and the clot retraction began after 3 hours. The hemoglobin concentration increased to 9.6 Gm. per cent and the erythrocyte count to 3.6 million. However, the capillary fragility remained increased.

Ten days later she began to develop toxemia of pregnancy. The blood pressure rose to 150/90, the urine contained 0.2 to 0.3 per cent albumin, and the blood uric acid rose to 4.5 mg. per cent. With increasing severity of the toxemia, and despite the continuation of prednisone, deterioration in the status of the I.T.P. occurred, with the appearance of petechiae and ecchymoses. Treatment with prednisone was therefore discontinued, and ACTH in a daily dosage of 80 mg. was begun. The toxemia progressed further, however, and the ocular fundi at this time showed hypertensive retinopathy, Grade 3, with fresh hemorrhages. The blood pressure rose to 190/120, albuminuria to 1.6 per cent, blood uric acid to 6.9 mg. per cent, and the serum total protein decreased to 5.4 Gm. per cent. The patient developed internal and external hemorrhages. There was bleeding into the lungs as evidenced by hemoptysis, and on x-ray a picture similar to that of bronchopneumonia was found. Bleeding into the wall of the uterus occurred and its size increased from that of a 7 months' to that of a 9 months' gestation. The uterus was hard but the fetal heart was audible. There was also massive hematuria. A blood examination showed 30,000 platelets and a bleeding time of more than 16 minutes. Clot retraction did not begin until after 24 hours.

The patient's condition deteriorated from hour to hour. She lost consciousness. The hemoglobin decreased to 6.5 Gm. per cent with 2 million erythrocytes. At this stage she was given 2 transfusions of fresh blood, followed by 2 transfusions of thrombocytes. ACTH was discontinued and prednisone in large dosages (100 mg. daily) was begun. This intensive treatment dramatically stopped all gross bleeding, but the toxemia became even more severe. One day after cessation of bleeding there was an eclamptic fit, and the patient was treated with magnesium sulfate and morphine. One day after the attack of eclampsia she was delivered of a male premature infant, weighing 1.4 kilograms. The delivery was normal with no more than the usual loss of blood.

Examination of the infant shortly after birth revealed a platelet count of 124,000. After 16 hours, however, the platelets decreased to 50,000, and the newborn began to bleed from the nose and vomited blood. He was treated with prednisone, 5 mg. per day, but died 3 days after birth. At autopsy there was jaundice of all tissues, hemorrhage in the falx cerebri and mucosa of the stomach. Rare foci of hematopoiesis in the liver and spleen were found.

Immediately after delivery marked improvement took place in the mother's condition, with progressive disappearance of the symptoms of toxemia. Clinical manifestations of the I.T.P. decreased, petechiae and ecchymoses ceased to appear, and the ocular fundi became normal, although the laboratory data were still abnormal. Ten days after delivery the blood pressure had decreased to 120/80, albuminuria to 0.1 to 0.2 per cent, blood uric acid to 3.5 mg. per cent, and the serum protein had risen to 6.4 Gm. per cent. Prednisone was gradually reduced from 100 mg. to a daily dosage of 20 mg., and 20 days after delivery was discontinued.

The first pathological hematological finding to disappear was the increased capillary fragility. The second sign to improve was the clot retraction, which began after 5 hours, although platelet count and bleeding time were still abnormal. When the patient was discharged in satisfactory condition 26 days after delivery, clot retraction had returned to normal. The anemia showed considerable improvement. The hemoglobin was 10 Gm. per cent and the erythrocyte count 3.7 million. However, the bleeding time did not return to normal until 4 months after discharge from the hospital, when the platelet count had risen to 90,000 where it has remained for more than half a year after delivery. With only this latter single indication of abnormality the patient resumed her daily routine activities. Menstruation, which returned 3 months after delivery, is normal.

Comment

This case fulfills the requirements for the diagnosis of idiopathic thrombocytopenic purpura. The persistence of thrombocytopenia for over 6 months after delivery rules out the possibility that it was secondary to any physiological, metabolic, or therapeutic mechanism connected with the pregnancy. The absence of a palpable spleen or of demonstrable autoimmune antiplatelet antibodies is not inconsistent with the diagnosis. Each of these manifestations is found in no more than a third of the cases of I.T.P.

The onset of I.T.P. during the patient's first pregnancy suggested the possibility that the pregnancy itself might have been responsible in some way for precipitating the first clinical manifestations of the disease. This possibility is supported by reports of women with more than one pregnancy, who during each pregnancy suffered from an exacerbation of their I.T.P.

Corticosteroid therapy, with its tendency to promote the retention of salt and water and to elevate blood pressure, should of course be avoided in pregnancy if at all possible. The use of prednisone in this patient to control purpura may have contributed to the rapid onset and severe course of the toxemia. The toxemia in turn may itself have induced the severe recurrence of I.T.P. that accompanied it. This possibility is supported by the fact that with delivery and cessation of the toxemia, the I.T.P. immediately began to improve to the point where therapy could be discontinued without the reappearance of clinical symptoms.

A mechanism whereby toxemia might aggravate thrombocytopenic purpura has already been described. Ward and MacArthur[4] found in 10 women with mild to moderate pre-eclampsia an average platelet count of 155,000, approximately that of normal pregnant women. In 6 patients with severe pre-eclampsia and 1 with eclampsia, however, the average was 97,000, with a range of 72,000 to 120,000. It seems likely that the thrombocytopenia of severe toxemia could potentiate the thrombocytopenia of I.T.P. and thus cause an exacerbation of the disease. Whether the mechanism whereby the platelet count in toxemia is reduced is related to the activity of an antiplatelet antibody system like that of I.T.P. is a matter for speculation, but it is known that antibody formation in pregnancy is more rapid than usual.

Purpura, unrelated to I.T.P., is known to occur during the course of eclampsia, but it is usually ascribed to liver damage. The temporary thrombocytopenia of severe pre-eclampsia and eclampsia reported by Ward and MacArthur might contribute to the appearance of this type of purpura, as well as to that of I.T.P. or purpura on any other basis.

The problem requiring further examination is that of administration of ACTH and cortisone in I.T.P. in pregnancy in general and in I.T.P. complicated by toxemia of pregnancy in particular. On the one hand, we know that these hormones have a beneficial effect on increased capillary fragility and an inhibitory effect on some antibodies; on the other hand, ACTH and cortisone are known to cause hypertension and water retention.

In the case described the patient was treated with both large dosages of prednisone and transfusions of blood and thrombocytes. The question of which treatment caused cessation of bleeding—prednisone, transfusions, or both—still remains open, but we are under the impression that ACTH and cortisone aggravated the toxemia and thereby endangered the life of the patient.

Since it cannot be foreseen whether a pregnant woman with I.T.P. may develop toxemia of pregnancy, ACTH and cortisone should be administered with considerable caution. This treatment should be stopped as soon as the first signs of toxemia of pregnancy appear.

The infant born to this patient showed a symptom complex and laboratory results similar to the mother's and despite prednisone treatment died from hemorrhages 3 days after delivery.

Summary

A case of idiopathic thrombocytopenic purpura in a primigravida is reported. The hemorrhagic diathesis was markedly exacerbated during an attack of severe pre-eclamptic toxemia which progressed to frank eclampsia. A mechanism whereby the toxemia might have caused this exacerbation is discussed. The problem requiring further examination is the administration of ACTH and cortisone in I.T.P. aggravated by toxemia of pregnancy.

We are indebted to Prof. B. Zondek for his helpful suggestions.

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FETAL WEIGHT ESTIMATION

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THE estimation of the weight of a fetus in utero is invariably not only difficult and inaccurate, but may be catastrophic because of gross errors in reckoning. Surprisingly, too, for information so important, simple observation and palpation are most commonly used rather than the more scientific mensuration. As far back as 1906, McDonald[1] advised against the use of such landmarks as the umbilicus and the ensiform process in estimating the size of the fetus, stating that "several thousand measurements were studied in the hope of reaching an average height of the umbilicus; but it was found to vary from 12 cm. to 20 cm. above the symphysis." Therefore he recommended the use of a tape measure to determine the height of the uterus. Despite this admonition more than fifty years ago, very few obstetricians use any kind of measuring device to aid them in the appraisal of the size of the fetus. Consequently, the latter is frequently under- or overestimated, resulting in a premature baby at elective cesarean section, or an overly large baby with consequent cephalopelvic disproportion in an apparently normal pelvis.

The most recent and ingenious methods for the estimation of fetal size are those of Poulos and Langstadt[2] and Johnson and Toshach.[3] The former used a pelvimeter to measure the vertical and horizontal diameters of the uterus. They then applied the mean of these two diameters, allowing for the thickness of the abdominal wall, to the formula for the volume of a sphere, $V = \pi/6D^3$. From a study of 45 patients in labor, they developed a formula for birth weight: $W = 1{,}870 + 0.11D3 \pm 250$. They found that in 68 per cent of their cases the predicted weight was within 250 grams of the actual weight.

Johnson and Toshach, using the McDonald method, measured the height of the fundus from the upper border of the symphysis over the convex surface of the uterus. They started with the empirical assumption that with the vertex at station 0 and the fetus weighing 7 pounds, 8 ounces the McDonald measurement would be 34 cm. and with each increase of 1 cm. in the McDonald measurement, the fetal weight would increase by 5½ ounces. They then devised the formula: baby weight = 7½ (M + S − O − 34) (5½ ounces). In this formula "M" is the McDonald measurement, "S" the station of the presenting part, and "O" the allowance for obesity (if the patient is over 200 pounds, subtract 1 cm.). The result of the calculation in the parentheses gives the number of ounces to be added to or subtracted from 7½ pounds to get the estimated birth weight. They claimed a standard deviation of 12.45 ounces and that 68 per cent

of all babies would be within that range. They concluded "more complicated ways of estimating birth weight have not proved statistically to be better than the method presented." More recently, Johnson[4] offered a further simplification of the above techniques by the following formulas:

$$\frac{\text{McDonald's} - 13}{3} = \text{fetal weight in pounds}$$

Or if the presenting part is at station 0:

$$\frac{\text{McDonald's} - 12}{3} = \text{fetal weight in pounds}$$

At a plus station, calculations are as follows:

$$\frac{\text{McDonald's} - 11}{3} = \text{fetal weight in pounds}$$

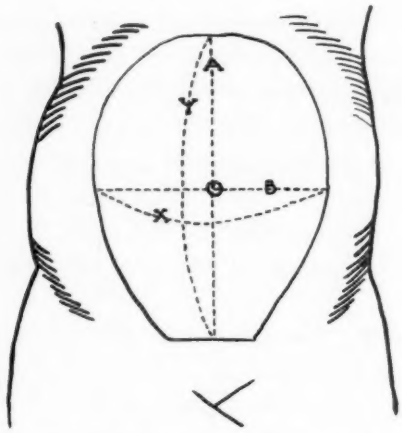

Fig. 1.—Diameters measured to estimate the size of the fetus. *A*, Vertical length with a caliper pelvimeter. *B*, Horizontal diameter with the pelvimeter. *X*, Horizontal diameter with tape measure. *Y*, Vertical diameter with tape measure.

Method

For several years I[5] have been measuring the vertical and horizontal diameters of the uterus, using both the pelvimeter and the tape measure, and from the sum total of these measurements the size of the fetus has been determined. It seemed logical, and experience has confirmed the conviction, that measurements derived from the use of both pelvimeter and tape measure were more accurate than data obtained by only one type of measuring device because of the errors created by distortion of the uterus. Laxity of the abdominal and uterine walls allows the fetus to be predominantly forward or to one side, thus altering the contour of the uterus which causes considerable error with the pelvimeter technique. The combined method compensates for this error. The measurements are taken weekly beginning 4 weeks before the expected date of confinement. The top of the fundus and the most lateral points on either side of the uterus, which are usually on the same plane as or a little above the umbilicus, are marked with a skin pencil. If the patient is obese, weighing over 150 pounds, the double thickness of the abdominal wall is measured by picking it up with the pelvimeter

and, if it is 2 cm. or more, the thickness is subtracted from each of the diameters. The following measurements are then taken, with each point of the measuring device pressed in firmly:

1. With the pelvimeter, the height of the uterus from the middle of the upper border of the symphysis, usually 27 to 29 cm. at term.

2. Again, with the pelvimeter, the horizontal diameter, from the most lateral point on one side of the uterus to a corresponding point on the other, usually 14 to 16 cm. at term.

3. With the tape measure firmly applied over the convexity of the uterus, the vertical diameter from the same two points as with the pelvimeter, usually 32 to 34 cm. at term.

4. Again, with the tape measure, the horizontal diameter with the same two points as with the pelvimeter, usually 24 to 26 cm. at term. If the head is engaged at station 0, add 3 cm. to each of the vertical measurements; if at station –1, add 2 cm.; at station –2, add 1 cm. The most accurate estimates are made with the head unengaged and the vertex level with the upper border of the symphysis. The method is not very satisfactory in breech presentation or in transverse lie. When this method was originally tried, if the total was between 95 and 105 the fetus was considered to be mature and of average size, that is, between 5½ and 7½ pounds. A total under 95 indicated a premature fetus and over 105, an excessively large baby, multiple pregnancy, or hydramnios. More recently, a chart has been improvised from a statistical survey with the use of this plan whereby the fetal weight may be reckoned more specifically.

Material

Data were compiled from observations on 500 unselected vaginal deliveries exclusive of breech presentation and transverse lie and 100 elective repeat cesarean sections. The patients were not in labor at the time of the measurements. The weight of the fetus at the time of the last mensuration was determined in retrospect by subtracting from the birth weight the amount gained in the interim according to Streeter's[6] chart which postulates a gain of 31 grams per day during the thirty-sixth to the thirty-eighth week, and 35 grams per day during the thirty-eighth to the fortieth week. The results are demonstrated in Tables I and II.

TABLE I. FETAL WEIGHT IN FIVE HUNDRED VAGINAL DELIVERIES

TOTAL OF 4 MEASUREMENTS	NO. OF CASES	MEAN WEIGHT	PREDOMINANT RANGE	LOWEST WEIGHT	HIGHEST WEIGHT
80-89	12	4 pounds, 12 ounces	4½ pounds to 5 pounds—100%	4 pounds, 8 ounces	5 pounds
90-94	87	5 pounds, 9 ounces	5 pounds to 6 pounds—80%	4 pounds, 14 ounces	6 pounds, 12 ounces
95-100	154	6 pounds, 10 ounces	6 pounds to 7 pounds—90%	5 pounds, 11 ounces	7 pounds, 10 ounces
101-105	188	7 pounds, 7 ounces	7 pounds to 8 pounds—88%	6 pounds, 9 ounces	8 pounds, 6 ounces
106-110	51	8 pounds, 4 ounces	8 pounds to 9 pounds—82%	7 pounds, 14 ounces	9 pounds, 8 ounces
Over 110	8	(5 sets of twins, 1 hydramnios, 2 excessively large babies weighing 10 pounds, 4 ounces and 11 pounds, 5 ounces, respectively)			

TABLE II. 100 ELECTIVE CESAREAN SECTIONS

TOTAL OF 4 MEASUREMENTS	NO. OF CASES	MEAN	LOWEST WEIGHT	HIGHEST WEIGHT
95-100	52	6 pounds, 8 ounces	5 pounds, 12 ounces	7 pounds, 4 ounces
101-105	48	7 pounds, 4 ounces	6 pounds, 8 ounces	8 pounds, 3 ounces

Results

Measurements taken during the thirty-eighth to the fortieth week were predominantly, 68 per cent, in the range of 95 to 105. In this range, 88 per cent of fetuses will be found to be of mature size, over 5½ pounds, but not of excessive size, not over 8 pounds. One hundred elective cesarean sections were done after maturity had been decided by this method and no babies under 5½ pounds were delivered. By the use of this technique to determine fetal maturity before elective cesarean section, an additional guarantee may be derived from measuring through the abdominal wall the occipitofrontal diameter of the fetal head as it lies at the pelvic brim. If the occipitofrontal diameter is 11 cm. and the range of uterine measurements over 95, maturity is practically certain.

Comment

Measurements should be taken routinely in all cases, beginning 4 weeks before term. The chart is then referred to for the weight range. When labor begins, the number of days elapsed since the last mensuration is multiplied by 31 if it is between the thirty-sixth and thirty-eighth weeks, and by 35 if between the thirty-eighth and fortieth weeks, to find the additional weight gain of the fetus. This is added to the last determined weight range to ascertain the probable weight of the baby to be delivered.

Summary

1. A method of estimating fetal weight in utero by both the pelvimeter and the tape measure is presented.

2. The combined technique corrects for distortion of the uterus and bizarre positions of the fetus.

3. Results are charted in 500 vaginal deliveries and 100 elective repeat cesarean sections.

4. The normal range for the total of 2 vertical and 2 horizontal measurements is 95 to 105.

5. The method has proved in my hands to be 88 per cent accurate for estimating a fetus of mature size in utero.

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PROLONGED RETENTION OF A DEAD FETUS

A Case Report

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IN NOVEMBER, 1957, Tricomi and Kohl[1] reviewed their experiences with retention in utero of dead fetuses. The data in their study supported the concept of conservative management and abstinence from interference in cases of prolonged retention of a dead fetus.

This case report is of a pregnancy which was terminated by cesarean hysterectomy 165 days after fetal death and in the fifty-sixth week of gestation. Several factors make the history of unusual interest.

The patient was a 36-year-old white single woman who was hospitalized continuously for schizophrenia throughout her pregnancy and so offered an unusual opportunity for close observation. She had obstetrical care in this institution and psychiatric care elsewhere.

She was first seen in our department on May 10, 1957. At that time she was considered to be about 18 weeks pregnant. The time of the last menstrual period was believed to be December, 1956, with the estimated date of confinement in October, 1957.

In the eighteenth week of gestation the blood pressure was 140/90. Rapid weight gain and edema occurred and in the twenty-sixth week the blood pressure was recorded as 150/100. Toxemia of pregnancy was diagnosed and gradual improvement followed the use of sedation, diet, and diuretics.

On Aug. 21, 1957, in the thirty-second week of gestation, the patient was normotensive, had no toxic symptoms, had 1 plus albuminuria, and was considered to be doing well. In the thirty-third week of gestation fetal movement ceased and fetal heart tones were not audible on Aug. 24, 1957. X-ray proof of death was obtained the following week. Induction of labor was attempted repeatedly with intravenous Pitocin with and without estrogen priming, as suggested by Robinson, Datnow, and Jeffcoate.[2] We noted complete lack of uterine response to Pitocin during the following weeks. The toxemia improved following death of the fetus.

After 6 weeks of care on the Obstetrical Service the patient was returned to her nearby psychiatric hospital and was followed at weekly intervals in our Obstetrical Outpatient Department. Eleven weeks following the death of the fetus, Pitocin inductions were again unsuccessful. During all this period of observation the cervix was short, firm, and closed. Because of the dangers of afibrinogenemia, repeated determinations of the fibrinogen level were obtained and were within normal limits.[3]

One hundred twenty-eight days after the death of the fetus, and after some deterioration in the patient's psychiatric state had occurred, it was felt that she must be delivered and we prepared to abandon our conservative management. The cervix could not be entered for amniotomy and a final course of Pitocin after several days of high estrogen dosage resulted in the same complete lack of uterine response. Our plans to perform cesarean section were postponed by the patient's escape from the hospital.

When she was located 5 days later she was noted to be febrile and the best efforts of the Obstetrical and Medical Departments could not account for the fever of 102-104° F. There was no abdominal tenderness or vaginal discharge. There was no leukocytosis. The patient, a schizophrenic Christian Scientist, had no complaints. Penicillin, tetracycline, and erythromycin had no effect on the fever. Abdominal x-rays showed absolutely no change in the fetus *five* months after its death.

In spite of the fever of unknown origin, laparotomy was finally performed on Feb. 7, 1958—165 days after death of the fetus, and in the fifty-sixth week of gestation. An intrauterine pregnancy was found in a partially necrotic uterus, perforation having occurred through the fundus. Intestines and omentum had collected in a mass over the perforation. The myometrium was riddled with abscesses. The uterus contained about 1,500 c.c. of pus which proved to be sterile. The oviducts and ovaries were not identifiable because of distortion (Fig. 1).

Cesarean section and complete hysterectomy were performed. Surprisingly, the fetus showed almost no maceration.

A remarkably benign postoperative course followed and the patient was discharged in good condition.

Fig. 1.—Appearance of uterus at laparotomy, intestines and omentum having been separated from the necrotic, perforated fundus.

Comment

Abstinence from interference in cases of prolonged retention of a dead fetus has been recommended.[1, 4] Lack of uterine response to Pitocin has been considered a sign of extrauterine pregnancy. The case reported here of retention of a dead fetus for 165 days leads us to question both of these concepts.

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THE EFFECTS OF ORALLY ADMINISTERED RH HAPTEN*

A Study of 17 Cases

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AS REPORTED previously,[1] we are investigating the effects of the Rh hapten given orally. This is obviously a long-term project, but initial observations concerning the results in regard to Rh antibody titer are of interest. The Rh hapten is a fraction obtained from Rh-positive red cells by means of fat solvents.[1, 2] This substance appears to neutralize Rh antibody both in vivo and in vitro. Previously it was administered intramuscularly, but for nearly two years it has been given by mouth.

Method

For oral administration, the fraction, dried to the consistency of petroleum jelly, is first weighed and then mixed with powdered lactose to the point where it can be handled easily. It is then rolled on a graduated pill tile and cut into aliquots, each containing not less than 100 mg. hapten. Each of the aliquots is taken up into a No. 2 gelatin capsule. Until they are dispensed, the capsules filled with hapten are kept refrigerated.

The capsules of Rh hapten are distributed on the request of the physician to Rh-negative women who have lost babies previously because of Rh incompatibility, but who are not yet pregnant at the time. The woman is instructed to take one capsule daily and her Rh antibody titer is observed at biweekly intervals. She is not accepted as an individual to whom to supply hapten unless our own laboratory and one other have demonstrated Rh antibodies in her blood. The patient is urged to avoid pregnancy until her Rh antibody titer is at zero. When this has been achieved (in from one to four months), her doctor advises pregnancy. As soon as she knows that she is pregnant, she is provided with sufficient hapten for a daily dose of from 100 to 200 mg., and this is continued until term. Physicians who have had experience with the Rh hapten have recommended that the pregnancy be allowed to go to term unless some extraneous reason contraindicates this. With the use of the hapten, prematurity is the hazard rather than exposure to Rh antibodies.

Results

Seventeen women have been provided with Rh hapten to be taken orally. Eight of these women have completed pregnancy. We are able to state, as we

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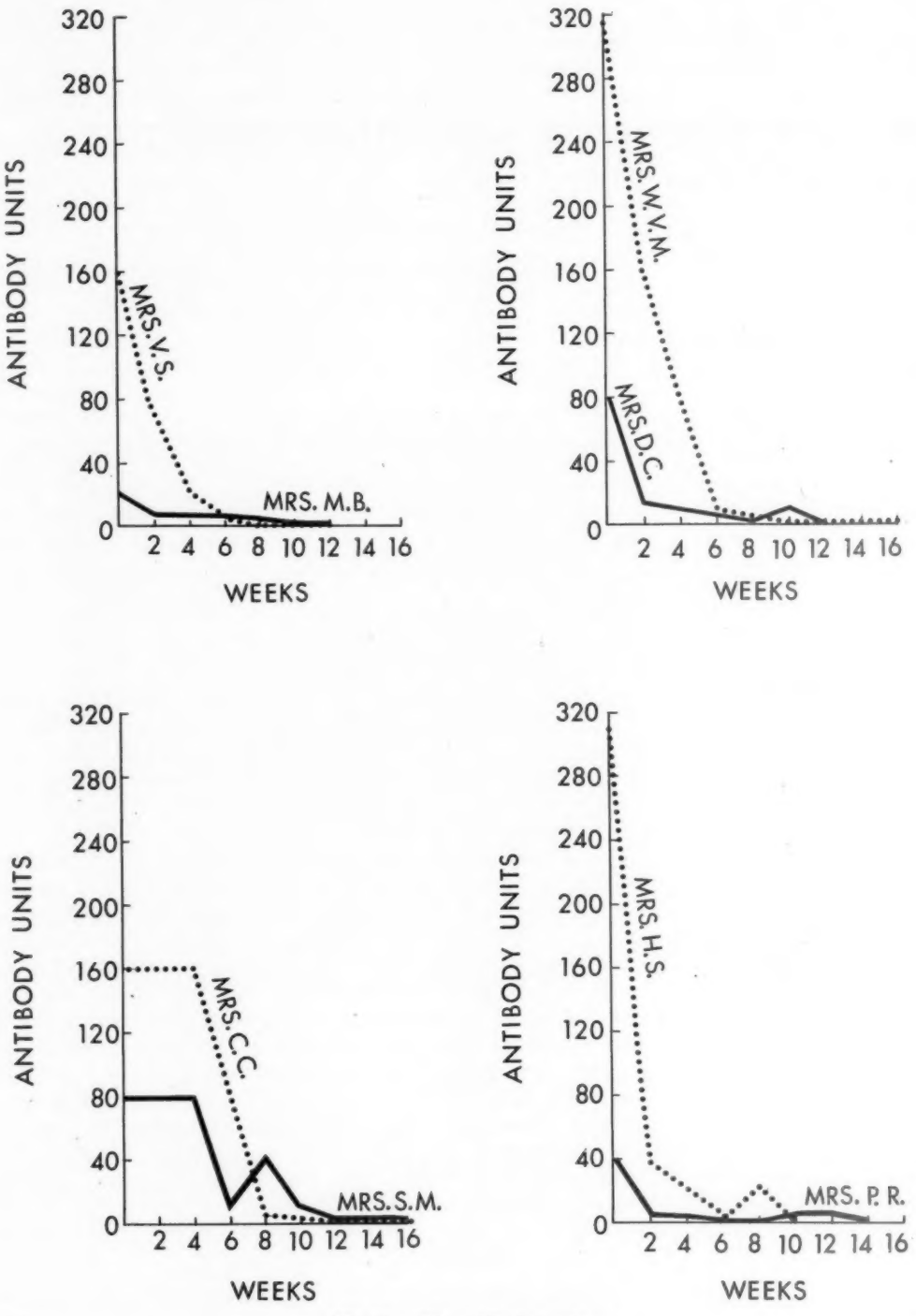

Fig. 1.—Rh antibody units.

did in 1956,[1] that there has been not one baby lost because of Rh incompatibility to a mother treated with the Rh hapten prior to pregnancy. In the single exception reported previously, further investigation disclosed that the pregnancy was terminated by the physician because of maternal high blood pressure, water retention, and anuria.

Our interest at present, however, is in the effect of orally administered hapten on the Rh antibody titer. Oral administration appears to be fully as effective as, if not more than, intramuscular injection. Each of the 17 women showed a fall in titer which reached zero, according to our methods of assay, in four months or less. This is illustrated by the antibody curves tabulated here (Fig. 1).

Summary

In summary, initial experience with Rh hapten given orally to 17 Rh-negative sensitized women indicates that this is an effective method of reducing Rh antibody titers.

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HEMATOMA OF THE UMBILICAL CORD

A Case Report

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REPORTED cases of hematomas of the umbilical cord, as a complication of pregnancy, are rare.[1, 2] In 1940, Dippel[1] reviewed the world literature and added 8 cases, which brought to 36 the number of such cases.

The rarity of this lesion prompted the reporting of the following case, which, to our knowledge, is the first to be reported since Dippel's review.

The patient was a 28-year-old woman, gravida i, para 0, whose expected date of confinement was Sept. 12, 1954, and whose last menstrual period occurred on Dec. 5, 1953. She was admitted to Walter Reed Army Hospital at 3:30 A.M. on Aug. 31, 1954, stating that the membranes had ruptured. There were no associated contractions or bloody show. The patient's prenatal course had been essentially normal. She was Rh positive and had a negative serologic test for syphilis.

Physical examination of the cardiovascular and respiratory systems was negative. The blood pressure was 120/70. Examination of the abdomen revealed a full-term intrauterine gestation. The fetus was in vertex presentation, with fetal heart tones of 140 located in the right lower quadrant. Sterile vaginal examination showed the membranes to be ruptured. The remainder of the physical examination was noncontributory.

The patient's early first stage of labor was uneventful. At 12:20 P.M. the cervix was completely effaced and 5 cm. dilated, the vertex being at a plus 1 station. At this time, on rectal examination, there was palpated a soft cystic mass presenting inside the cervix alongside the infant's head. Vaginal examination was performed and inside the cervix a 4 by 2 cm. fixed cystic mass was felt over the right parietofrontal area of the skull. It was thought that this represented a cephalhematoma. Labor progressed normally and at 3:56 P.M. the patient was spontaneously delivered of a full-term living female infant. A median episiotomy was used to facilitate delivery. The placenta was then delivered spontaneously and intact. Examination revealed a cystic dilatation of the cord. After a normal postpartum course, both the patient and the infant were discharged from the hospital. *At no time was there fetal distress during the first or second stage of labor.*

Gross examination of the placenta showed that it measured 15 cm. in diameter. The fetal surface had a normal, smooth, glistening appearance. Examination of the maternal surface disclosed the cotyledon pattern to be essentially intact throughout. There was a 60 cm. length of umbilical cord attached to the placenta. Approximately 15 cm. from the placenta there was a fusiform enlargement of the cord which measured 8 by 4 cm. (Fig. 1). The contents appeared to be composed of clotted blood. No abnormalities of the remaining cord were identified.

Microscopic examination of multiple sections of the umbilical cord revealed that the umbilical arteries were contracted, with no apparent abnormality present. Examination

of the vein, however, showed it to be moderately dilated with a minute point of rupture. The hematoma seemed to be of recent origin. Hemorrhage into Wharton's jelly was continuous with that of the lumen of the vein. Pathologically, the cause of rupture of this vessel could not be determined on microscopic examination.

Comment

The incidence of hematomas of the umbilical cord is considered to be approximately one in 5,505 deliveries.

In the studies to determine the etiology of hematomas of the umbilical cord, syphilis, mechanical trauma, anomalies of the umbilical veins or arteries (degenerative or congenital), short cords, cord around the neck, torsion of the cord, and ruptured membranes have all been incriminated. There is, however, no really adequate explanation.

According to Dippel, hematomas of the cord are usually single and arise from the umbilical vein. They vary in size from 1.3 cm. to "the size of a child's arm" and, although usually located near the umbilicus, they may be located anywhere along the cord.

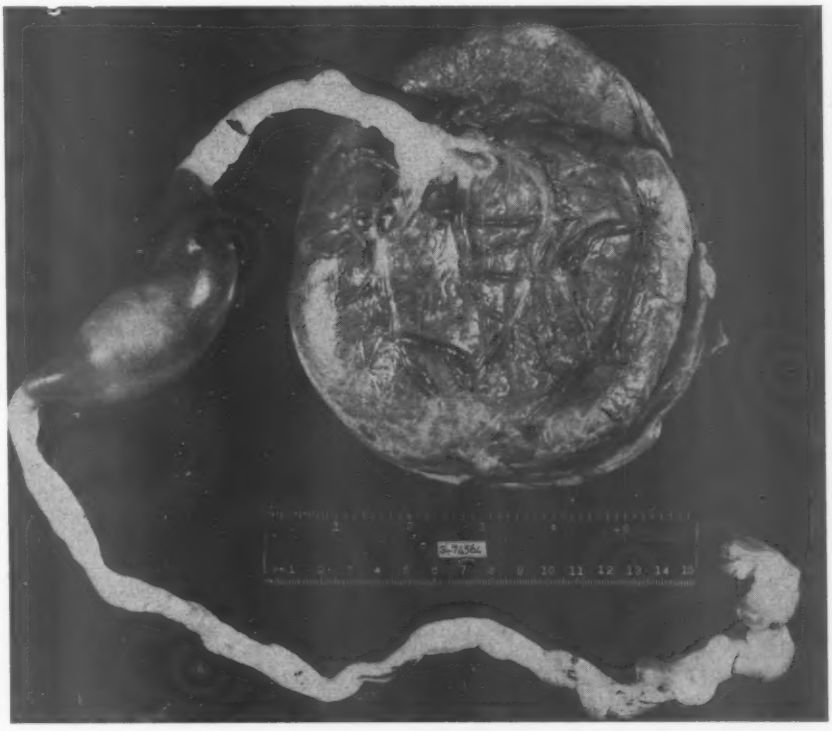

Fig. 1.—Photograph of umbilical cord and placenta showing location and relative size of hematoma.

The fetal mortality rate is reported to be 47 per cent, with the majority of deaths occurring in the first or second stage of labor.

In our patient, the hematoma must have developed in the first stage of labor, but, although detected at that time, it was misinterpreted. From an

etiological viewpoint, one can theorize that the loop of cord, either low lying or occultly prolapsed, must have become traumatized between the fetal and maternal tissues. The complete absence of detectable fetal distress, however, is of considerable interest. If further hemorrhage had occurred, fetal death might have ensued from compression of the remaining umbilical vessels by the increasing hematoma.

Summary

An additional case of a hematoma of the umbilical cord has been reported. The birth of a living infant in the presence of a low-lying cord with a hematoma and without clinical evidence of fetal distress makes this an unusual case.

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APPENDICITIS DURING PREGNANCY

An Unusual Case

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APPENDICITIS is recognized as one of the more important surgical complications of pregnancy. The reported fetal loss has been from 20 to 40 per cent and the maternal mortality is in the neighborhood of 5 per cent.[1] The incidence of appendicitis in pregnancy is believed to be the same as in the nonpregnant, and is variously given as 0.1 to 0.5 per cent.[2] It is one complication of pregnancy in particular in which prompt diagnosis permitting early surgical intervention is mandatory, as rupture of the appendix doubles the risk of abortion[1] and jeopardizes the life of the mother.

It is generally agreed that the symptoms are the same as in the nonpregnant except for the location of pain. The belief is widely held that the pain may be higher and more to the side because of the upward displacement of the head of the cecum with advancing pregnancy.[2] In the last trimester the appendix is presumed to rise above the level of the iliac crest and, accordingly, the pain may be expected considerably higher than the level of the acetabulum as is usual in the nonpregnant.[2]

The following case is presented to show how reliance upon this presumption may contribute to a false conclusion.

A 24-year-old gravida ii, para i, who was 6 months pregnant, was admitted to the hospital because of progressively severe low abdominal pain of 3 days' duration. She had had two atypical menstrual flows following her recent conception, and had complained of heartburn for two weeks prior to admission. The progress of this pregnancy otherwise had been uneventful.

Her one delivery, which took place 2 years before, had been unremarkable except for a pelvic infection, apparently salpingitis, which developed a week following confinement. It required rehospitalization for several days and subsided after 6 weeks.

During the 3 days immediately preceding admission, the patient experienced generalized abdominal soreness and intensification of the epigastric distress. Her appetite and bowel functions were normal. On the third day the soreness became most prominent in both lower quadrants. It was dull and constant but apparently not severe enough to keep her from going to work.

Physical examination upon admission revealed an acutely distressed patient who appeared moderately ill. The blood pressure was 118/80 mm. Hg and the pulse rate 86 per minute. The temperature was 99.8° F. Enlargement of the abdomen corresponded with that in the sixth month of pregnancy. The hypogastric and iliac regions were tender on palpation and moderate guarding was noted which appeared at least partly voluntary.

Costovertebral angle tenderness, present bilaterally, was more pronounced on the right. Rectal examination elicited extreme tenderness which was not localized to either side, and there was no impression fullness in the cul-de-sac.

Initial laboratory studies showed a hemoglobin of 11.0 Gm. per 100 c.c., a white blood count of 19,100 with a shift to the left, and 15 to 25 white cells per high-power field of catheterized urine.

On the basis of the physical findings, the conditions presenting themselves for differentiation were pyosalpinx and appendicitis. Pyuria can occur because of the proximity of an inflamed appendix or other pelvic appendage to the ureter or bladder, and it was felt that the acute clinical picture could not be attributed to the pyelonephritis which that laboratory finding suggested. The region of maximal abdominal tenderness was situated 2 inches below McBurney's point. This decidedly low location, together with the history of antecedent pelvic infection, favored the impression of pyosalpinx.

The patient was given large doses of antibiotics, parenteral fluids including 1 pint of blood, and progesterone.

In the ensuing 2 days, the temperature fluctuated between 98.8 and 99.8° F., and re-examination of the white cells and urine showed no significant changes. There was no obstipation but a flat plate of the abdomen showed considerable air scattered throughout the bowel, suggesting the possibility of ileus. The patient complained of increasing pain and required more medication for relief.

A ruptured appendix or pyosalpinx was suspected, and 48 hours following admission a laparotomy was performed through a right midrectus incision. A walled-off mass was found in the lower right side of the abdomen about an edematous cecum which was not displaced above its usual site in the nonpregnant patient. Incorporated in the pus-containing mass were a massively perforated gangrenous appendix and a large fecalith several centimeters removed. An appendectomy was performed and adhesions involving the right Fallopian tube were cut.

The postoperative course was remarkably good, and the patient was able to leave the hospital 10 days following operation. The uterus was quiescent throughout the illness, including the time of actual operation. Two months later, at what was estimated to be the thirty-eighth week of pregnancy, the patient was delivered of a normal child weighing 7 pounds, 4 ounces.

Comment

The possibility of an acute condition within the abdomen complicating pregnancy calls for careful evaluation with a minimum of delay. While laparotomy may precipitate abortion or premature labor, postponement of surgical intervention carries the risk of an inflamed appendix proceeding to rupture, with attendant greater threat to the life of the mother and fetus. The lessening of the danger of localized or generalized peritonitis from rupture of the appendix by antibiotic therapy is not sufficient to justify a policy of watchful expectancy nor to minimize the urgency of prompt diagnosis permitting early operation.

In the case presented the patient was 6 months pregnant and, in accordance with the generally accepted changes in position of the appendix with advancing pregnancy, the pain was to be expected at about the level of the iliac crest. Since it was actually suprapubic, the diagnosis of appendicitis appeared less likely.

Eastman[2] stated, "Our own observations lead us to believe that the appendix may be situated at a considerably higher level in some cases while in

others it is found at the usual site.'' This case supports the view that displacement of the cecum is not sufficiently consistent to constitute a rule of probability in the differential diagnosis of acute abdominal conditions complicating pregnancy, and suggests that undue reliance upon presumed changes in location of appendiceal pain is best avoided.

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BACTEREMIC SHOCK ASSOCIATED WITH PSEUDOMONAS SEPSIS AND STILLBIRTH

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INFECTION with *Pseudomonas aeruginosa* is rare. Still more rare is pregnancy with a related infection due to this organism. This report is submitted on the basis of pure cultures of the Pseudomonas organism isolated from maternal urine and lochia immediately post partum, and from fetal tissues obtained at autopsy. Unfortunately, maternal blood cultures were not obtained at the proper time to substantiate the clinical impression of bacteremia. Additional interest is provided by the hypotension plus the leukemoid reaction that appeared shortly after the institution of antibiotic therapy.

Pseudomonas sepsis in obstetrics had been reported on 4 occasions prior to 1956. In December of that year Stough and Shinner[1] reviewed the literature and cited 2 additional cases. In an extensive search of the literature, we have been unable to uncover any further cases of maternal Pseudomonas infection, nor have there been cases previously described with the hypotension and marked leukocytosis reported in this presentation.

Pseudomonas aeruginosa, frequently referred to as *Bacillus pyocyaneus,* is a gram-negative, motile bacillus. It is normally found in small numbers in the human digestive tract and skin, and is often found in air and water.[2] It is therefore easily available as a contaminant of wounds and medical instruments.

With widespread use of antibiotics, relatively nonpathogenic organisms such as the Proteus, Coliform, Pseudomonas groups and the Candida organisms, i.e., Monilia, have become more prevalent invaders. Such infections are more likely to occur if antibiotics are administered prophylactically for long periods or at frequent intervals in mixed infections.[3] The more susceptible bacteria are thus eradicated and the resistant gram-negative forms are allowed to emerge. Stanley[4] has pointed out that in adults the Pseudomonas most commonly gains access to the blood stream via urinary tract infections. In the gravid patient, placental[5] as well as gastrointestinal[1] and urinary tract origins have been proved.

Case Report

Mrs. J. W., No. 57-12306, a 27-year-old para ii-0-0-ii, whose estimated date of confinement was Jan. 19, 1958, was admitted to the isolation labor room at Flushing Hospital on Nov. 4, 1957, 10½ weeks from term, in active labor. The membranes had been ruptured for 22 hours.

One week prior to admission the patient developed afebrile tonsillitis for which she received symptomatic treatment. Four days prior to admission she had attempted to take a douche. While inserting the nozzle she encountered pain and withdrew the nozzle without douching. Within an hour a bloody discharge was noted on the underclothes. The last prenatal visit was normal and the fetal heartbeat had been heard. At 8 A.M. the day before admission the membranes ruptured spontaneously. While on bed rest the watery discharge was noted to be "brown, then greenish yellow and foul smelling." At 7 P.M. a shaking chill and fever of 102.6° F. developed. She was placed on antibiotics, aspirin, and fluids, by her private physician. Within 2 hours the temperature was 103.6° F. and there had been two episodes of vomiting. Uterine contractions started at 4 A.M. with the appearance of a bloody discharge. The patient denied marital relations for at least a week before the onset of the present illness.

When first seen the patient was in the labor room, a foul odor quite evident. A precipitate frank breech delivery of a 1,490 gram stillborn, macerated male infant and intact placenta and membranes occurred 50 minutes after admission. The lochia and placenta were foul smelling and the membranes were edematous and friable. The blood pressure was 100/60 and the temperature 99.6° F.

An infusion of 500 mg. tetracycline was started on admission. The blood count reported at this time showed 27,000 white cells, with 74 segmented cells, 11 stab cells, and 15 lymphocytes. The hemoglobin was 10.5 per cent and the erythrocyte count was 3.67 million. The blood type was B, Rh positive, and the Wassermann test had been reported previously as negative. A blood culture was ordered, the tetracycline doubled, and a second infusion of 5 million units of aqueous penicillin started. The patient was observed with frequent blood pressure, pulse, and temperature determinations.

Two hours after delivery the blood pressure suddenly dropped to 60/30, the pulse was weak and thready, and the facies was drawn. Methoxamine hydrochloride, 20 mg. intravenously and 20 mg. intramuscularly, was given with poor response. A 4 c.c. ampule of levarterenol in 1,000 c.c. of 5 per cent glucose in water was then started. This dose had to be tripled before the desired effect could be obtained. Hydrocortisone, 100 mg., was also administered at this time. Further examination disclosed no evidence of hemorrhage or abnormalities other than a questionably enlarged liver. There was no adenopathy or splenomegaly. The patient was well hydrated although she was vomiting and unable to tolerate oral medication. The temperature was now 99.0° F., the white count 46,000 with 52 segmented cells, 44 stab cells, and 4 lymphocytes. Cultures had been obtained of blood, lochia, and urine. The hematocrit was 39 per cent, erythrocyte count 4.0 million, and the icterus index 7.4. It was decided to continue steroid therapy and 100 mg. of additional cortisone was given during the next twelve hours, followed by 25 mg. at 6 hour intervals. The tetracycline was continued, 500 mg. every 6 hours, and aqueous penicillin, 1 million units every 4 hours, until culture and sensitivity tests were available. Vasopressors were necessary for the next 18 hours to maintain a systolic pressure of 90 mm. Hg. Urinary output for the first 12 hours post partum was limited to 100 c.c. This gradually increased during the next 6 hours, by which time a good urinary output was well established, and the vasopressors were discontinued.

The white count continued to rise and show a shift to the left until a peak was reached at 11:30 P.M., 17½ hours post partum. The total count was then 71,800, with 52 segmented cells, 29 stab cells, 15 metamyelocytes, and 4 myelocytes. The red count and hematocrit remained unchanged.

In view of the family history of leukemia (the patient's father had died of "cancer of the blood"), during the next 24 hours a bone marrow aspiration was obtained, as well as a battery of liver function tests, electrocardiogram, and chest x-ray. The results of all these tests were normal.

On the third postpartum day, the patient was able to tolerate oral feedings and medication. Cultures of the urine, lochia, and fetal lung tissue were reported positive for Pseudomonas. There was also reported a *Staphylococcus albus* contaminant in the lochia. The blood culture was negative. While the patient was on the tetracycline therapy, repeat

urine cultures were sterile so that, when sensitivity studies indicated nitrofurantoin to be the most specific antibacterial agent, the tetracycline was continued and the nitrofurantoin added to the regimen. The patient was now ambulatory for short periods, and management of the case resolved itself to adjustment and reduction of steroids, maintenance of antibiotics, and supportive nutritional therapy.

On the fourth postpartum day the blood pressure remained steady at 110/70 and, although the patient complained of weakness and occasional bouts of vertigo, her condition was rapidly improving. The leukocyte count, followed closely for the duration of the hospital stay, fell progressively in total count with a gradual return to a normal differential.

Upon discharge, 16 days after delivery, the white count was 14,000, with 71 segmented cells, 4 stab cells, and 25 lymphocytes. The urine remained negative. Nitrofurantoin therapy was continued for an additional week at home.

Comment

Hall and Gold[6] have reported a mortality of 51 per cent in a study of 35 patients with shock associated with bacteremia due to different species of organisms. Death in 6 of these cases was ascribed to terminal oliguria and uremia. The authors point out that gram-negative bacteria were indicted in two thirds of the cases as the causative agents. Martin and Nichols,[7] in an excellent discussion of "circulatory collapse in less esoteric bacteremias," cited the coli-aerogenes group of organisms, and reviewed experimental data applied to the problem of shock. They pointed out that, although the exact mechanisms are not known, endotoxins affecting the vascular system directly,[8] or indirectly through central vasomotor paralysis,[9] have been demonstrated. Other work has suggested that the altered hemodynamics of the liver is chiefly responsible for similar hypotension in experimental dogs.[10] A "therapeutic paradox" resulting in hypotension has been suggested, in which large amounts of bacterial endotoxin are released from bacteria rapidly destroyed by large doses of antibiotics (Jarisch-Herxheimer reaction).[6] Studdiford and Douglas,[11] reporting 7 cases of bacteremic shock, called attention to clinical developments similar to those seen in cases of septic abortion. The coli-aerogenes group were again isolated from nearly all cultures. Placental lesions characterized by bacteremia of the fetal vessels were found in their severe cases. They stressed the significance of concentration of bacteria, after fetal death, in a location poorly reached by antibiotics. In addition, this report noted one death due to the Waterhouse-Friderichsen syndrome.

One can only speculate as to the pathogenesis of this case. It is felt that there was no relationship to the antecedent tonsillitis. Since that infection was not treated by antibiotics, the emergence of the Pseudomonas from a treated mixed infection can be ruled out. The attempted douche leading to trauma may be significant. It is possible that a contaminated douche nozzle served as the agent directly depositing the organisms within the maternal tissues, with the subsequent development of the apparently infected secundines. Although the placenta and membranes appeared grossly infected, it is unfortunate that they were discarded in haste without benefit of pathologic and bacteriologic investigation. Blood cultures obtained after administration of massive antibiotic therapy were not helpful. However, the isolation of the organism in the urine, lochia, and fetal lung tissue following the infectious course described justifies classification of this case as bacteremia. It is felt that the placenta was the focus of bacterial growth, presenting a source of bacteria and endotoxins to the maternal and fetal systems. The rapid and complete withdrawal of this focus was apparently responsible for a clinical course less severe than should have otherwise been expected.

The sudden hypotension encountered was originally interpreted as a symptom of possible impending adrenal failure. Consequently, steroid therapy was instituted early. Adrenal steroids do not inhibit the growth of bacteria. They exert an anti-inflammatory and antitoxic effect. There is no evidence that steroids, when properly administered, interfere with antibody formation.[12] Their use is justified in fulminating cases where a marked diminution of toxicity may be achieved, prior to the natural mobilization of immune bodies and endogenous adrenal action.[13] The literature appears to confirm our observation that steroid hormones do not seem to lessen the shock.[6, 7, 11] There is an equal uniformity of opinion as to results obtained with the use of vasoconstrictors. Methoxamine and levarterenol have been demonstrated as most effective in treating bacteremic shock.[6] In our case, we found the hypotension to be most resistant. Once adequate renal filtration was assured and the urinary output satisfactory, the vasoconstrictor was discontinued, but not until the fourth postpartum day did the blood pressure become stabilized at 110/70.

With resort to corticoid therapy, potent antibiotics must be used concomitantly to counteract the anti-inflammatory effect of the hormone. The specific antibiotic to combat *Ps. aeruginosa* infection is Polymyxin B.[14, 15, 16] Because of side effects including circumoral and digital paresthesia, not uncommon cerebellar ataxia, and the capability of this drug of causing renal damage, one may resort to other antibiotics for parenteral administration. Oxytetracycline is the next most effective drug. It is somewhat more effective than tetracycline against many strains.[14] Penicillin is not effective at all. The strain isolated in our case proved most sensitive to nitrofurantoin. Fortunately, the focus had been expelled and the infection was well under control with tetracycline, prior to the addition of nitrofurantoin to the therapeutic regimen.

In closing, mention is made of the degree of leukocytosis. The peak count of 71,800 white cells and the shift to the left producing 19 per cent myelocytic forms bear testimony to the severity of the infection. Very likely the fortunate outcome, in this age of wonder drugs, was largely the result of the patient's sensitive and responsive reticuloendothelial system.

Summary

1. A case of *Pseudomonas aeruginosa* sepsis with stillbirth is presented, along with sequelae of bacteremic shock and leukemoid reaction.

2. Antibiotics effective in such infection are mentioned.

3. The case is discussed in relation to current etiological and therapeutic concepts of bacteremic shock with comment on the use of adrenal steroids and vasoconstrictors for such a complication.

4. Note is made of the increased prevalence of infections due to gram-negative organisms and their relation to bacteremic shock.

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POSTPARTUM INVERSION OF A UNICORNUATE UTERUS

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INVERSION of the uterus is a dramatic, although rare, complication of parturition. Statistics on its incidence range from one in 4,753 to one in 8,883 pregnancies in reported series. The object of this paper is to present a case of inversion of the uterus 9 days post partum, associated with a unicornuate uterus and congenital absence of the left kidney, ureter, tube, and ovary.

Case Report

I. M., a 27-year-old gravida i, para i, whose last menstrual period was Dec. 10, 1955, was admitted to the Rhode Island Hospital on Sept. 30, 1956, complaining of an exquisitely tender mass protruding from the vagina. Nine days prior to admission she had been delivered of a full-term living female infant, weighing 6 pounds, 12 ounces, at another hospital. Her labor had begun about 8 A.M. on Sept. 20, 1956, and progressed slowly with severe pain requiring frequent sedation. She was taken to the delivery table at 2:30 P.M. on Sept. 21, 1956, after 30 hours of labor. Three hours later she was delivered of the baby spontaneously over a right mediolateral episiotomy. The patient stated that she was awake and remembered that following the delivery the nurse pushed quite hard upon her abdomen. She began to complain of lower abdominal pain and, with some difficulty, the third stage of labor was completed. After returning to her room, she had a bout of heavy bleeding for which she was given 500 c.c. of blood. At 1:30 P.M. on Sept. 22, 1956, 8 hours after delivery, she bled again and went into mild shock, requiring another 500 c.c. of blood. After this, she did well for a short time, but the next day she complained of back pain and rectal discomfort and needed codeine for relief. When she was out of bed she noted what she described as "pressure" on the perineum.

She was discharged from the hospital on the fourth postpartum day, still having a small amount of vaginal bleeding. Four days later she noted pelvic discomfort and a moderate amount of bleeding. She was given Ergotrate without effect. The pain and bleeding persisted. She also was unable to void. On Sept. 30, 1956, she noted a mass protruding from the vagina. She passed some clots, and the pain increased, and her temperature rose to about 101° F. She was then hospitalized.

Examination showed an acutely ill young woman, with a temperature of 100.2° F., pulse of 100, blood pressure of 170 systolic, 90 diastolic. She was unable to extend or adduct the legs. The abdomen was distended and tender in both lower quadrants. There was a large, tender, beefy-red mass, 10 by 10 cm. in size, protruding from the vagina. It was covered with a foul exudate, fibrin, and clots. The episiotomy was separated and infected.

The hemoglobin was 9.2 Gm. per 100 c.c. of blood, the leukocyte count 19,000, and the hematocrit 30 per cent.

On admission the patient was given 500 c.c. of whole blood. A catheter could not be passed into the bladder. Three hours after admission she was taken to the operating

room and, under spinal anesthesia, a catheter was finally inserted into the bladder and 800 c.c. of urine was obtained. In the lithotomy position manual replacement of the mass by taxis was unsuccessful due to a tight ring of constriction above it. The lower abdomen was prepared and entered through a midline incision. The uterus was seen with a deep dimple at the fundus with only the right tube and ovary visible in it (Fig. 1).

The successive applications of tenacula resulted in successful recovery of the inverted fundus. No incision in the uterine muscle was required. It was then noted that

Fig. 1.—Inital findings at laparotomy, showing deep dimple in fundus, and only one tube and one ovary protruding.

Fig. 2.—Hysterosalpingogram, 5 months after operation, confirming unicornuate uterus and absent left tube.

the uterus was large, unicornuate, and without a left tube and ovary. Exploration of the upper abdomen revealed the absence of the left kidney and a hypertrophied right kidney. After excision of a myoma of the round ligament on the left, and appendectomy, the abdomen was closed. During the procedure the patient received an additional 50 c.c. of whole blood.

Postoperatively the patient ran a low-grade fever for 2 days but then had an uneventful recovery and was discharged on the ninth hospital day. At the time of this report, 12 months following her delivery, the patient is feeling well, and has regular and painless menstrual periods. Her only concern is a fear of recurrence of the inversion in subsequent pregnancies.

Intravenous pyelography confirmed the absence of the left kidney and a hysterosalpingogram some weeks later confirmed that the uterus was unicornuate with a single patent right tube (Fig. 2).

Comment

Etiologically, 30 to 40 per cent of inversions of the uterus are spontaneous, although many factors have been discussed. Poor management of the third stage of labor with undue traction on the umbilical cord, pulling on the placental site with its underlying flaccid musculature, is prominently mentioned. Too vigorous manual pressure on the fundus of the uterus, severe straining on the part of the patient, and manual removal of the placenta are other factors.

We here would suggest another, though admittedly rare, provoking cause—congenital abnormalities.

In the treatment of subacute inversion of the uterus efforts at vaginal replacement by taxis are frequently rewarding, but more commonly one must resort to the Spinelli operation, or some abdominal procedure which employs traction as its fundamental principle. The abdominal approach was successful in this case, and no incision in the region of constriction was necessary.

Summary

A case of subacute inversion of the uterus on the ninth postpartum day, associated with congenital agenesis of the left Müllerian and Wolffian systems, is presented. Consideration must be given to the possibility that these anomalies may have contributed to the inversion which occurred.

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HEMATOMA OF THE RECTUS ABDOMINIS MUSCLE SIMULATING RUPTURE OF THE PREGNANT UTERUS*

A Diagnostic Problem

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SPONTANEOUS hematoma in the rectus abdominis muscle or within its sheath during pregnancy is of considerable clinical interest because of the rarity of the condition and the diagnostic puzzle which it often presents. A correct preoperative diagnosis is infrequently made, even though in retrospect the signs and symptoms are so constant that diagnosis should be easy.

That the clinician should be familiar with this disease entity is borne out by a reported maternal mortality rate of 12 to 15 per cent and a fetal mortality rate of 25 to 50 per cent,[1, 2] indicating that this is potentially a hemorrhagic catastrophe of the third trimester of pregnancy.

Case Report

Mrs. J. V., a para ii, abortus i, gravida iv, housewife, was first seen in the third month of her fourth pregnancy, at which time pelvic examination disclosed a mass 4 cm. in diameter at the cervicoisthmic junction, anteriorly on the right, presumably a uterine myoma.

Two years earlier, 3 months after a spontaneous abortion, the uterus had been found to be irregularly enlarged by a right cornual mass 10 cm. in diameter, believed to be a myoma. Because of the patient's strong desire for more children a myomectomy was performed, a solitary 9 by 8 by 8 cm. intramural myoma being excised from the right anterolateral uterine wall. She subsequently did well except for recurrent episodes of bronchitis.

Following her initial prenatal visit and after reviewing the records of the previous uterine operation, it was decided to deliver her electively by cesarean section at approximately 39 weeks' gestation.

Except for a troublesome cough, thought by a medical consultant to be due to chronic allergic bronchitis, her prenatal course was uneventful until the thirty-second week when, during a coughing spell, she noted the sudden onset of severe right mid-abdominal pain which grew steadily worse. There was no vaginal bleeding.

When she was first seen, 2 hours later, she was pale and apprehensive, and was complaining of severe abdominal pain. Her pulse was 100 and blood pressure 105/60. There was marked tenderness over the entire right side of the abdomen with moderate contralateral tenderness. No masses other than the gravid uterus of a size compatible with a 32 weeks' gestation were apparent. The uterus was not notably irritable, the fetal heart tones were regular and of good quality, and the fetus could be palpated lying longitudinally, the vertex floating above the pelvic brim.

*This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

Because of the history of extensive uterine surgery, impending rupture of the uterine scar was felt probable. The patient was transfused and a laparotomy was performed, revealing a large hematoma in the right rectus muscle which contained an estimated 500 c.c. of fresh and clotted blood. This was evacuated, the muscle was retracted, and the inferior epigastric vessels were identified. An actively bleeding point of rupture of the vein was noted and both vessels were ligated. Intraperitoneal exploration was then carried out, revealing the uterus to be intact with a well-healed right cornual scar with no apparent thinning. The right subfascial space was drained with a Penrose drain brought out through a right lower quadrant stab wound and the midline incision was closed in layers. The postoperative course was uneventful and the patient did well during the remainder of her pregnancy.

Delivery of a viable 6 pound, 15 ounce male infant was accomplished by low cervical cesarean section at 39 weeks' gestation. The anterior rectus sheath on the right was noted to be somewhat thickened. Only minimal thinning of the right cornu of the uterus was noted. A myoma 5 cm. in diameter was excised from the anterior, lower uterine wall on the left. The postoperative course was again uneventful and both mother and infant have subsequently done well.

Comment

Cullen and Brödel,[3] in 1937, clearly delineated the anatomy of the rectus abdominis muscle in a classic monograph which has been the basis for subsequent studies of diseases of this structure. The muscle, divided at intervals by ligamentous septa into four muscle bellies, is covered by a strong tendinous sheath in its entirety except for the lower posterior one third where the muscle fibers are in close approximation to the peritoneum. Between the muscle and the peritoneum in this region run the large inferior epigastric artery and vein with their branches which penetrate the two lower muscle bellies and anastomose with descending branches of the superior epigastric vessels, whose branches penetrate the two upper muscle bellies.

Because of the absence of a posterior sheath in the lower one third of the muscle a hematoma spreading downward to this exposed area causes peritoneal irritation and symptoms of intra-abdominal disease, frequently leading to diagnostic confusion.

Pregnancy has long been recognized as an important predisposing factor in the pathogenesis of spontaneous hematomas of the rectus abdominis muscle. Teske,[4] in a review of 100 cases collected from the literature since 1900, found that 22 occurred in association either with late pregnancy (16 cases), labor (3 cases), or the immediate puerperium (3 cases). It has been suggested,[5, 6] and certainly seems probable, that overstretching of the muscle fibers during pregnancy may increase the susceptibility to trauma.

Precipitating causes most commonly cited include chronic cough,[1, 2, 7] strain of labor,[1, 8] systemic disease such as typhoid fever and influenza,[8, 9] and direct trauma,[10, 11] as shown in Table I. By far the most common factor is severe paroxysmal coughing. In cases associated with typhoid and influenza there appears to be an increased tendency to muscle degeneration, thereby predisposing to rupture during the strain of labor.

TABLE I. PRECIPITATING FACTORS IN HEMATOMA FORMATION DURING PREGNANCY

Cough	18
Labor strain	6
Fall	2
Typhoid fever	1
Influenza	1
Spontaneous	1
Not stated	9
Total	38

Diagnosis.—Of paramount importance is keeping the possibility of hematoma in mind. Analysis of the 38 cases reviewed emphasizes that this is a disease of older multiparas, the average age being 32 and the parity v.

The onset, typically, is abrupt and follows a paroxysm of coughing. Pain and tenderness are marked and usually localized to the area of the hematoma, but may be generalized. Over 90 per cent of the hematomas occur unilaterally in the lower half of the muscle. Nausea, vomiting, and some degree of shock are common. Muscle spasm and hyperesthesia over the involved rectus is marked, and a mass confined to the affected muscle sheath can, if looked for, usually be detected. If the patient lifts her head from the pillow so as to contract the rectus, the mass can be felt confined to the rectus sheath and immovable.[12] Ecchymotic discoloration of the skin over the hematoma and around the umbilicus is cited as a diagnostic sign, but is of debatable value early in the course of the disease. The uterus is of normal size for the dates and the fetal parts are usually easily felt. Table II records the initial diagnoses entertained in the cases reviewed.

TABLE II. INITIAL DIAGNOSIS IN 38 CASES OF HEMATOMA OF THE RECTUS ABDOMINIS MUSCLE DURING PREGNANCY

Suspected hematoma	11
Twisted ovarian cyst	6
Abruptio placentae	4
Rupture of uterus	3
Pedunculated myoma	2
Muscle hernia	1
Extravasation of urine	1
Acute cholecystitis	1
Ruptured hydatid cyst	1
Diagnosis undetermined	8
Total	38

Treatment.—Operative exploration with evacuation of clots, ligation of bleeding vessels, and closure of the fascia, with and without drainage, have been the usual procedures employed. At times[1, 13] the hematoma has not been evacuated at the time of laparotomy because of extensive organization, and healing has been relatively uneventful.

Torpin, on the basis of his personal experience and review of the literature, recommended conservative management, including (1) correct diagnosis, (2) rest in the recumbent position with relief of the intermittent strain of coughing and of labor by proper sedation, tight abdominal binder, and ice bags, (3) blood transfusions to replace loss and prevent shock, and (4) possible administration of blood coagulants. This program undoubtedly will suffice for smaller hematomas, not associated with rupture of one of the major epigastric vessels. In the presence of signs and symptoms of continuing hemorrhage, however, operation is necessary to achieve hemostasis.

The advisability of providing for postoperative drainage will depend upon the extent of the hemorrhage, the degree of hemostasis that can be obtained in the muscle, the size of the dead space, and the opinion of the individual surgeon. In general, it is felt that drainage is the conservative approach and of possible prophylactic value in preventing abscess formation or a persistent tender mass, although Sheehan advises against drainage.

Prognosis.—High maternal and fetal death rates have been noted ever since publication of the earliest cases. The patient reported upon by Hobbs[14] died in less than an hour after the onset of symptoms, before transfusions could be given. In Torpin's series of 28 cases, reported in 1943, the maternal

mortality was 15 per cent and the fetal mortality 50 per cent. Sheehan reported a maternal mortality of 12 per cent and fetal mortality of 25 per cent.

The great majority of maternal deaths occurred before the widespread availability of adequate blood replacement facilities. In the 10 cases (including the present case) reviewed which have been reported since Torpin's series, there has been no maternal death and only one fetal death attributable to this complication.[2, 5, 13, 15, 16, 17]

Summary

1. A case of hematoma of the rectus abdominis muscle during pregnancy which simulated rupture of the uterus has been presented and the pertinent literature has been reviewed.

2. The similarity of the symptoms in the cases reviewed indicates that, if the possibility is kept in mind, particularly in the older multipara afflicted with severe coughing spells, correct diagnosis should present no great difficulty.

3. The indications for and some of the practical aspects of conservative and surgical management of the condition have been presented.

4. Although this is a potentially serious cause of third trimester hemorrhage, early recognition and prompt treatment should greatly increase maternal and fetal survival.

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INTRAPARTUM LATERAL X-RAY IN THE CONDUCT OF DYSTOCIC LABORS

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THIS study was undertaken to assay the value of intrapartum x-ray pelvimetry in the management of dystocia. The etiological factors which make for dystocia are familiar. In an effort to differentiate them and to plan therapy accordingly, we have come to rely in part on the lateral x-ray during labor, often repeated two or three times at intervals. With such help during dystocic labor more accurate weight can be assigned to factors such as bony disproportion, malpresentation, inertia, and soft-tissue dystocia. Furthermore, it was believed that Pitocin augmentation of labor in indicated cases could be more safely and widely employed if the intrapartum lateral x-ray showed no bony disproportion as a contraindication to its use.

When the new maternity pavilion was constructed at The Mount Sinai Hospital in 1952, a fully equipped x-ray facility was placed on the delivery floor close by the labor rooms. The x-ray machine is constructed to utilize target-film distances of 72 and 54 inches according to the technique described by Wolf and Loevinger.[1, 2] This technique allows direct measurement from the films of the various pelvic planes with the use of a calibrated centimeter ruler with a 92 per cent correction scale for x-rays taken at 72 inches and an 86 per cent correction scale for x-rays taken at 54 inches.

The x-ray machine is sufficiently sturdy and foolproof so that the obstetrical resident staff after minimal instruction can take, develop, and measure their own films. This permits full use of this aid in the management of difficult labor during the full 24 hours.

Fifty cases of dystocia in which a lateral x-ray was taken during labor have been submitted to analysis. These cases comprise approximately half of the patients so evaluated in 1954 to 1956. One lateral view was taken during labor in 39 cases, two lateral views in 7, and three in 4. When more than one film was made during labor, they were taken several hours apart. The large majority of the 50 patients had had x-ray pelvimetry during the antepartum period because it was suspected clinically that some degree of pelvic contraction was present.

It is appropriate to record the average figures for the pelvic diameters and the lower limits of normal according to the technique employed by Wolf and Loevinger (Table I).

TABLE I. AVERAGE AND LOWER LIMITS OF NORMAL PELVIC DIMENSIONS

	AVERAGE NORMAL (CM.)	LOWER LIMIT OF NORMAL (CM.)
Inlet anteroposterior	11.5	10.3
Inlet transverse	12.	11.3
Pubosacrococcygeal	12.	10.3
Interischial	11.	10.3

We regard the interischial diameter as the transverse diameter of the midpelvis. The interspinous diameter, though traditionally reported, is regarded as unimportant because it is almost always posterior to the center of the pelvic cavity, the larger diameters of the head descending anterior to the spines. Furthermore, the length of the spines strongly affects the interspinous diameter and yet long spines do not greatly influence the course of labor since their very length takes them further posterior to the center of the pelvic cavity.

For illustrative purposes, Table II represents a labor profile of the 11 patients who had more than one film taken in labor.

The 50 dystocic labors may be divided into three broad groups according to etiology. There were 13 cases in which faulty attitude of the vertex was contributory, 38 in which pelvic dimensions were reduced, and 9 in which the baby was unusually large. As can be noted from the total, more than one factor was operative in 10 of the 50 cases.

Ineffectual contractions further complicated 24 labors. In 26 the contractions were good and labor was not stimulated. The 24 patients in whom labor was stimulated received intravenous Pitocin in drip dilution of 0.5 to 1 c.c. of Pitocin to 500 c.c. of glucose in water, the solution usually running at 16 to 20 drops per minute. Eighteen patients so treated were delivered vaginally. The duration of Pitocin stimulation varied from ½ to 12 hours in all but one, Case 7. Her total labor of 71 hours was stimulated on three occasions by Pitocin, the aggregate length of its use being 31½ hours. She had a successful vaginal delivery. Six of the patients in the inertia group were delivered by cesarean section. Pitocin stimulation was continued into the second stage in 19 of the 24 patients; all but one of these were delivered vaginally.

Two tetanic contractions of the uterus were encountered in the Pitocin group. The first, ascribed to the relatively rapid infusion of the Pitocin solution, lasted 3 minutes. Pitocin was discontinued, but restarted 40 minutes later without incident. The second tetanic contraction resulted in significant slowing of the fetal heartbeat which was not relieved when the tetany disappeared and prompt cesarean section was performed at which the cord was found to be tightly around the baby's neck.

As illustrations of the method, films from 3 of the cases are reproduced, and the labor records detailed.

J. H., No. 29947, an 18-year-old nullipara, had x-ray pelvimetry first taken after 15 hours of labor, at which time the cervix was 5 cm. dilated, the head clinically unengaged and the vertex in a posterior position. The anteroposterior diameter of the inlet was 11.2 cm. and the transverse 11.7 cm. The interischial diameter was 10.7 cm., the bispinous 9 cm., and the pubosacrococcygeal 11.3 cm. The upper sacrum was flat, reducing the anteroposterior diameter of the superior midpelvis. There was no progress for 8 more hours and with gradual weakening of the contractions, intravenous Pitocin was started. After 2 hours of intravenous Pitocin the cervix was 9 cm. dilated. There was much molding clinically, but a lateral film showed that the biparietal diameter had failed to descend below the well-defined linea innominata (Fig. 1). Clinically there was some progress in anterior rotation and it was decided to administer intravenous Pitocin for an additional hour. At the end

TABLE II. LABOR PROFILE OF PATIENTS WHO HAD MULTIPLE LATERAL FILMS TO DELINEATE THE PROGRESS OF LABOR

CASE NUMBER	PATIENT	HISTORY NUMBER	PARITY	POSITION	NUMBER OF LATERAL FILMS	DILATATION WHEN HEAD FIRST ENGAGED	INLET AP (CM.)	INLET TRANSVERSE (CM.)	INTERISCHIAL (CM.)	INTERSPINOUS (CM.)	PUBOSACRO-COCCYGEAL (CM.)	STAGE I (HOURS)	HOURS I.V. PITOCIN DURING FIRST STAGE	STAGE II (HOURS)	HOURS I.V. PITOCIN DURING SECOND STAGE	DILATATION AT THE TIME OF CESAREAN SECTION (CM.)	TYPE OF DELIVERY	WEIGHT OF BABY (GRAMS)
1	E. M.	41371	0	ROP	2		10.4	12.7	11.7	10.4	11.8	26				5	Cesarean section	3,410
2	I. P.	20421	0	ROT	3	6 cm.	10.3	11.7	11.5	9.7	10.1	35		3	3		Barton midforceps	3,520
3	J. H.	29947	0	ROP	3	Full	11.2	11.7	10.7	9.0	13.0	26	3	2	2		Low forceps	2,940
4	A. S.	38566	0	LOT	3	8 cm.	10.4	12.2	10.8	9.9	12.2	20	2	1	1		Low forceps	3,750
5	O. I.	29972	0	LOT	2	8 cm.	9.5	10.9	10.0	9.3	10.4	11½		2¼			Low forceps	2,860
6	D. J.	29881	0	ROP	2	7 cm.	10.2	11.2	11.0	9.9	11.6	10		1½			Normal spontaneous	3,110
7	A. G.	64150	0	LOT	3	8 cm.	11.5	12.0	10.6	8.9	11.5	71	30	1½	1½		Barton midforceps	3,850
8	A. W.	71258	0	ROT	2	8 cm.	10.9	12.9	11.6	9.8	10.6	30	5	2¼	2¼		Barton midforceps	3,400
9	H. S.	53990	0	ROT	2	6 cm.	10.8	12.7	11.2	9.7	11.2	14		4½			Barton midforceps	3,550
10	C. R.	81660	0	LOT	2	7 cm.	10.2	12.0	10.8	8.7	11.8	45	10	¾	¾		Barton midforceps	3,830
11	M. W.	38571	0	ROP	2	8 cm.	11.5	11.6	11.4	9.4	11.4	16		1			Kielland midforceps	3,670

of this time, a second lateral film (Fig. 2) was taken. This showed real progress and vaginal delivery was anticipated. After a 2 hour second stage, during which Pitocin stimulation was continued a 2,940 gram baby was delivered in good condition by an easy low forceps operation. The total duration of labor was 28 hours, during the last 5 hours of which intravenous Pitocin was administered in dilute drip.

Fig. 1. Fig. 2.

Fig. 1.—Case 3 in Table II. Lateral film in a nullipara at 9 cm. dilatation of the cervix shows advanced molding as plane of obstruction is met. The linea innominata is well delineated and the head unengaged despite intravenous Pitocin stimulation.

Fig. 2.—Case 3. Second film taken 1 hour after preceding illustration shows descent and increased molding.

A. S., No. 38566, was a 23-year-old nulligravida. X-ray pelvimetry which had been done in the antepartum clinic revealed a flat sacrum directed posteriorly. The minimum anteroposterior diameter of the inlet was 10.4 cm., and the transverse 12.2 cm. The pubosacrococcygeal diameter was 12.2 cm., and the interischial normal. Despite the adequate pubosacrococcygeal measurement, the flattened upper sacral segments compromised the anteroposterior dimensions of the upper midpelvis. The patient was admitted 10 days beyond term with intact membranes, the presenting part at minus 2 station, the cervix 2 cm. dilated, and irregular contractions. After 12 hours of labor the membranes ruptured spontaneously and the first standing lateral film (Fig. 3) was taken. The head was noted to be in direct transverse, unengaged and not well flexed. It was entering the inlet in an optimal relationship, but overriding of the sutures was prominent. The cervix was dilated 8 cm. at this time, the head not well applied to the cervix. Eight hours later, with the cervix essentially unchanged, and the presenting part clinically unengaged, a second standing lateral film (Fig. 4) was taken. This showed engagement. Molding and overriding were both more noticeable. Since the minimum diameter of the pelvis had been traversed, it was decided to administer

Fig. 3. Fig. 4. Fig. 5.

Fig. 3.—Case 4 in Table II. Moderate molding is shown as the vertex meets obstructing planes at the inlet and upper midpelvis. The cervical dilatation was 8 cm. at this time.

Fig. 4.—Case 4. Film taken 8 hours after Fig. 3 shows increased molding and descent though the cervix was unchanged.

Fig. 5.—Case 4. After 2 hours of intravenous Pitocin stimulation the molded head was on the perineum.

intravenous Pitocin. After 2 hours of intravenous Pitocin, a third film was taken (Fig. 5). The head was well down; low forceps delivery of a living 3,750 gram baby in good condition followed shortly. Molding was marked and the biparietal diameter at delivery measured 8.5 cm.

M. W., No. 38571, a 25-year-old nullipara, was admitted in labor at term. On clinical measurement she was found to have a small pelvis. Routine pelvimetry showed a gynecoid pelvis with flat upper sacral segments and a poor sacral curve. The measurements of the inlet were: anteroposterior 11.5 cm., transverse 11.6 cm.; midpelvic measurements were pubosacrococcygeal 11.4 cm., interischial 11.4 cm., and bispinous 9.4 cm. Four hours after admission the cervix was 7 cm. dilated, the membranes ruptured, and the presenting part right occipitoposterior at minus 2 station. At this time the first standing lateral film (Fig. 6) was taken. The second lateral film (Fig. 7) 2 hours later showed increased molding but no change in the amount of overriding of the skull bones. There had been significant descent and after one hour in the second stage, since the patient was running a low-grade fever, a Kielland midforceps delivery of a 3,670 gram baby was performed. On the second postpartum day the infant's biparietal measurement was 9.4 cm., and the suboccipitobregmatic 9.8 cm.

Fig. 6. Fig. 7.

Fig. 6.—Case 11 in Table II. Unengaged head in a nullipara with the membranes ruptured and the cervix 7 cm. dilated. The position is right occipitoposterior.

Fig. 7.—Case 11. Second film taken 2 hours after Fig. 6 shows descent, molding, and some rotation. Shortly afterward midforceps rotation and delivery were accomplished.

Comment

Intrapartum pelvimetry has proved a most useful tool in the conduct of labor in patients who present dystocia problems, particularly problems originating from cephalopelvic disproportion. Lateral films in labor contribute valuable information by delineating the size of the fetal skull in relation to the obstructing

plane of the pelvis, the degree of flexion, the position, and the extent of molding and overriding. From the fetopelvic relations, particularly when comparison is made with a second film several hours later, a more accurate prognosis can be made, resulting in more definitive management than would otherwise be justified. In the occasional case where the pelvis is anthropoid with convergent side walls, an outlet view during labor may be important in ascertaining the degree of dystocia from the diminished transverse midpelvic dimensions.

In cases which cause doubt as to whether or not vaginal delivery is possible and in which the uterine contractions are suboptimal, an x-ray is a reliable guide to the safety or danger of Pitocin stimulation.

During a Pitocin-stimulated test of labor in cases of borderline cephalopelvic disproportion it must be emphasized that an operating room for cesarean section should be available at all times. Under such conditions the test of labor may be discontinued for either fetal or maternal indications and abdominal delivery done without delay. In the 24 cases in this series in which Pitocin was used, there were no untoward incidents except for the 2 tetanic contractions previously described.

Intrapartum pelvimetry has practically eliminated the trial of forceps on the obstetrical service of The Mount Sinai Hospital. This is a step in a conservative direction. With the aid of Pitocin in bringing the head down and the use of x-ray to show the accurate level of the biparietal diameter, the ease or difficulty of instrumental delivery can be more accurately gauged.

In undertaking Pitocin stimulation for borderline disproportion, advantages accrue from being able to telescope a test of labor. The shortening of labor is of great importance and, as is well recognized, influences the perinatal mortality. Also, where there is borderline disproportion, sedation is frequently withheld in order not to diminish the force of contractions, but the use of analgesic medication in adequate amounts is often feasible and even desirable when intravenous Pitocin stimulation is employed.

Cesarean Section Versus Vaginal Delivery.—Of the 50 patients with dystocia, 16 were delivered by cesarean section, 6 having previously undergone stimulation of labor by intravenous Pitocin for periods of up to 12 hours. In all 6, lateral films during labor indicated that a safe vaginal delivery might be anticipated. Unsatisfactory progress dictated abdominal delivery, however. Ten patients of the series, whose labors were terminated by cesarean section, did not receive antepartum Pitocin stimulation, either because the uterine contractions were believed excellent or because it was obvious from the lateral films that vaginal delivery was most unlikely even after optimal uterine action.

Thirty-four of the 50 patients were delivered vaginally, 18 of these receiving antepartum stimulation, 16 without stimulation.

Fetal Results.—There were 2 perinatal deaths in the 50 cases, one infant delivered by cesarean section, the other vaginally.

In the first case the patient was a 17-year-old nullipara who was said to be separated from her husband. The cervix became fully dilated after 16 hours of labor. At this time, the presenting part, a vertex in transverse position, was just above the spines, but it was the opinion of one of the members of the attending staff that it could be pushed deeply into the pelvis with fundal pressure. The estimated weight of the fetus was 3,200 grams. After 2 hours of full dilatation with ruptured membranes and no progress, a standing lateral film was taken. This showed the vertex at minus 1 station in left occipitotransverse. There was moderate molding but no overriding and there seemed to be some room posteriorly. In view of the patient's age and uncertain marital status, a junior consultant decided to allow a longer second stage. Caput became more marked but there was no actual descent and after 8 hours of second stage a low-flap cesarean section was done with delivery of a 3,760 gram

baby. In retrospect, it is difficult to understand why such a greatly prolonged second stage was permitted; it is not compatible with normal clinic policy. Though born alive, the baby did poorly and was thought to have central nervous system damage; he died on the third day. At autopsy, there was gross and microscopic evidence of nervous system congestion, pulmonary edema, pulmonary congestion, atelectasis, and a cephalhematoma.

In the second case, intrapartum fetal death occurred in a multipara who claimed to have delivered babies of 9 pounds, 11 ounces, and 11 pounds in Puerto Rico. After 2 hours of second stage she was delivered by a difficult DeWees extraction from midpelvis. Trouble was encountered with the shoulders and the 4,360 gram infant was stillborn. At autopsy there was adrenal and periadrenal hemorrhage.

The remaining 48 babies born after dystocic labors showed no discernible difference in their hospital course from that demonstrated by other normal babies.

It is pertinent to note that only one lateral film was taken during the labor in the 2 cases which terminated in fetal loss. In the case in which the baby had nervous system damage and died on the third day, the lateral film was taken very late, after full dilatation had already been present for 2½ hours. Further experience has indicated that lateral films are most useful if taken soon after progress comes to a standstill. In some cases a second or third film taken after an interval will be an important guide to management. It should be noted that the 2 cases which terminated in fetal loss were not among the 24 in which Pitocin stimulation was used. In all the Pitocin-stimulated cases, the babies did well.

Summary

1. In 50 patients with problems of dystocia, intrapartum standing or reclining lateral films were taken on the labor floor and provided valuable information as to the cause of the dystocia and the plane of obstruction.

2. In 11 cases a series of films provided a graphic guide to progress or lack of progress during labor.

3. The use of intravenous Pitocin to stimulate labor in 24 of the 50 patients avoided undue prolongation of labor, at the same time permitting adequate amounts of analgesic medication.

4. There were 2 fetal deaths in the series. There was no maternal morbidity or mortality.

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DYSTOCIA AND OCCIPITOPOSTERIOR

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THE confinement of Princess Charlotte of Wales with its far-reaching repercussions struck the medical world and the British Empire with the impact of a thunderbolt. The outcome of this labor was to jar the foundation of nineteenth century obstetrics with such force that it would never again entrench itself and become so arbitrary and resistant to change.

Since this case is a medical classic and has been pieced together only after painstaking research over a one hundred year period, I feel that it is a most appropriate introduction to our discussion on dystocia.

Princess Charlotte of Wales was 21 years of age at the time of her confinement, and heiress to the throne of Britain. The attending medical staff included Sir Richard Croft, the accoucheur, Dr. John Sims, the consultant, Dr. Mathew Baillie, the Royal Physician, and Sir Everett Home, Sergeant Surgeon to the King.

About 7:00 P.M. of Monday, Nov. 3, 1817, 42 weeks after her last period, the bag of waters ruptured and labor started.

At 11:00 P.M. Croft examined and found the cervical os 2 cm. dilated. The pains were coming every 8 to 10 minutes, but were weak. On Tuesday, Nov. 4, at 3:00 A.M., Charlotte was seized with a violent attack of retching.

From whatever cause, the pains continued mild during the first 24 hours. Although the pains continued weak, they were sharp, acute, and distressing, at intervals of about 8 minutes with but little advance of the labor.

At 11:00 A.M., after 16 hours, the cervical os was 6 cm. dilated with thin margins. At this point, Croft became concerned because of the slow progress and the irregular action of the uterus. Deeming consultation advisable, he wrote a letter to Sims, but delayed sending it when the pains improved.

Croft made another examination at 6 P.M. (Tuesday, November 4) and found that the os showed only an anterior lip. The labor progressed and at 9:00 P.M. the os was completely dilated.

Croft must now have had a feeling of great relief. In spite of poor pains, the first stage had lasted only twenty-six hours, the head was low, and Charlotte was well. Nevertheless, since the pains remained unusually feeble, he sent his note to Sims summoning his immediate attendance.

Sims arrived at 2:00 A.M. on November 5, after the second stage had lasted 5 hours. He was informed of the situation and declined a presentation to the

Princess but elected to remain in the next room where he was told regularly of the progress of labor. Instruments were in readiness, but the employment of them was never in question.

From about midday on Wednesday, November 5, after the second stage had lasted 15 hours, the uterine discharge became a dark green color, which made the medical attendants suspect demise of the fetus.

At between 3:00 and 4:00 P.M., the second stage having lasted 18 hours, the head began to bulge the perineum and at 9 P.M. the child was delivered spontaneously.

The child, a 9-pound boy, was dead and had evidently been dead for some hours.

To sum up the labor at this point, the delivery had lasted 50 hours, 26 hours of first stage and 24 hours of second stage, including 5 to 6 hours of perineal bulging. The second stage pains had been no more efficient than the first.

The Third Stage.—About 10 minutes after the birth of the child, Croft found that the uterus was still acting irregularly. He informed Sims that he suspected hourglass contraction with the placenta in the upper part, for he could not feel the placenta and the uterus remained high. They agreed that nothing should be done unless bleeding started. In another 20 minutes, she did bleed, and Sims agreed that the placenta should be removed. The hourglass configuration was confirmed. The upper segment was entered with slight difficulty and the remaining two thirds of the adherent placenta was peeled off without much difficulty. Blood loss was slight to moderate.

Immediately on its being separated, Charlotte complained of violent pains (the strongest pain in the whole labor) and the upper part of the uterus contracted on his hand. Croft grasped the placenta and gradually brought it down into the vagina. Leaving it there, he went again to Sims and the Council and reported what he had done. On returning he found Charlotte complaining of pains which recurred at intervals, and when these had continued to 10 o'clock, or about 25 minutes from the time the placenta was left in the vagina, he removed it. This was followed by a moderate discharge of blood. At this time, the uterus appeared moderately contracted. Charlotte appeared quite well after so tedious a labor, she took plenty of nourishment, and made few complaints, and had a pulse rate not exceeding 100. Croft felt no apprehension.

But at about a quarter to twelve, there was a change. She became a little sick and complained of a singing noise in her head, so he gave her a little camphor mixture which she shortly afterward brought up.

About a quarter to one (November 6) she complained of great uneasiness in her chest and great difficulty in breathing. The pulse became rapid, feeble, and irregular. She became extremely restless. The most active support by cordials, nourishment, antispasmodics, and opiate medicines was given. This very alarming state continued and kept increasing until, at half past two in the morning, 55 hours after labor started, Charlotte died.

At postmortem examination, the uterus was found to contain a considerable quantity of blood and extended as high as the navel, and the hourglass contraction

was still very apparent. The child was well formed and every part of its inner structure was quite sound.

Croft felt that the symptoms were similar to those that precede death from hemorrhage, though his estimated blood loss did not appear unusual.

The management of Charlotte's labor must be judged in the light of the midwifery practice of that day. The chief criticism is that Croft allowed labor to go on so long without using forceps. But by the principles and rules of contemporary practice, he was not wrong. To realize the astonishing degree of conservatism that prevailed at the time, one must read the standard textbooks.

Croft was trained by the renowned Denman, whose assistant he became, whose daughter he married, and whose practice he inherited. Denman's famous book, *An Introduction to the Practice of Midwifery,* first published in 1788, was a sort of obstetrical bible. Denman's law stated: "A practical rule has been formed, that the head of the child shall have rested for six hours as low as the perineum before the forceps are applied, though the pains should have ceased during that time."

Croft acted strictly according to Denman.

Three months later, the triangle was completed when Croft deliberately shot himself. He was emotionally disturbed and depressed at the blame and criticism cast upon him. That is why Sir Eardley Holland,[1] the eminent British obstetrician who had devoted considerable time to reconstructing the intimate details of this maligned case, described it as a "Triple Obstetric Tragedy"—mother, baby, accoucheur, all dead, all victims of a mistaken system of midwifery practice.

Hellman,[2] in his article, "The Duration of the Second Stage of Labor," described this tragedy of errors as a graphic portrayal of the blind faith in nature and the supine inactivity of the obstetricians of that day.

DeLee[3] maintained that labor cannot be called a normal physiologic function, that bodily damage of some degree always attends it even though this may be nothing more than the invariable pelvic floor injury. We agree that every labor, no matter how easy it may be, should be conducted with the same care and aseptic precautions that are devoted to major surgical procedures.

The medical attendant should never take the attitude of regarding labor as a simple, physiologic process to which he condescends to lend his assistance, but rather should look upon it as a procedure which may present emergencies to tax his best surgical, medical, and obstetric skill and judgment, often without warning.

Dystocia may arise from maternal or fetal causes, or from both combined. The course of labor is influenced by three main factors: (a) the efficiency of uterine contractions and the voluntary expulsive forces—the *powers;* (b) the size and position of the child—the *passenger;* (c) the size and shape of the pelvis—the *passage.* Therefore, we are at the mercy of the three P's—the powers, the passenger, and the passage.

We are here primarily concerned with occipitoposterior as a cause of positional dystocia.

Occipitoposterior Position

Etiology.—The causes of occipitoposterior are not outlined in most textbooks because they are considered to be mere accidents in rotation during advanced labor. Caldwell and Moloy[4] have shown that different varieties of pelves have characteristic modes of engagement of the vertex and mechanisms of labor which correspond. For example, in the android type, if the head engages in the transverse position, the prominent sacrum and narrow posterior pelvis force it forward into the narrow anterior position. In order to utilize the available space, it must assume the posterior position and so permit the smaller frontal diameter to adapt itself in the narrow anterior portion of the inlet. In the anthropoid pelvis with its contracted transverse diameter, engagement is possible only in the anterior-posterior diameter, and if the head passes the inlet in the posterior position, difficulty in its rotation may be expected. If this pelvic type is recognized, delivery can be effected with greater ease by delivery of the head with forceps in the posterior position, as it is mechanically wrong to attempt the rotation of the fetal head from a wide diameter through a narrower one.

Caldwell and Moloy suggested a dictum which describes the principles of engagement of the fetal head in the various pelvic types, "The fetal head in its descent attempts to adapt itself to the diameter of the inlet most suited for its reception." It is likewise important not to forget that the soft parts of the pelvic floor play a role in the mechanism of labor second only to that of the bony pelvis.

Incidence.—The frequency of occipitoposterior seems to vary considerably in various clinics throughout the country (Table I from Reddoch's[5] article), apparently depending on the time at which the diagnosis is made. This will no doubt account for our low incidence of 5.2 per cent, since we give ample time for spontaneous rotation (Table II).

TABLE I. FREQUENCY OF OCCIPITOPOSTERIOR POSITIONS*

	VERTEX	OCCIPITOPOSTERIOR	%
Hutchinson (Tulane)	150	49	32.67
Charity	798	136	17.04
Bodek	1,785	514	29.9
Danforth	1,137	285	25.1
Hill	927	204	21.1
Scott	1,000	144	14.4

*From Reddoch.[5]

TABLE II. FREQUENCY OF OCCIPITOPOSTERIOR PRESENTATIONS AT QUEEN OF ANGELS HOSPITAL, 1952 THROUGH 1956 (5 YEAR PERIOD)

	NO.	
Multiparas	590	
Primiparas	370	
Elderly primiparas	160	
Total	1,120	5.2 per cent of all deliveries

Prophylaxis.—Patients should be screened for possible dystocia on the first antepartum visit. In the large feminine or gynecoid type of pelvis, there is a minimum of difficulty during delivery. In the small gynecoid type, there is a higher incidence of dystocia than in the first group. In the android or male type and the anthropoid or apelike type, the incidence of occipitoposterior is

high. Careful bimanual examination adds specific knowledge concerning the pelvis and soft tissues. Roentgen pelvimentry is done when contracted pelvis is suspected.

Diagnosis.—Diagnosis is made by a combination of abdominal, rectal, and vaginal findings. The majority of occipitoposterior positions are right positions, so that the condition should be suspected whenever the back is found on the right or well into the flank and the small parts are near to the front on the opposite side.

Vaginal examination, which is much more conclusive than rectal, discloses the posterior fontanelle to be posterior in the pelvis, if it can be reached, and the large quadrilateral fontanelle is found anterior. The caput sometimes interferes with these findings and, in that event, the fingers should be passed to the side of the child's head to palpate the tragus of the ear which always points to the occiput. The posterior ear is the more readily located.

One diagnostic point that is often overlooked is that, in inspection of the abdomen, a concavity is present above the symphysis, if the bladder is empty and the abdominal wall not too fat.

Mechanism.—The mechanism of normal labor must be kept in mind at all times if the essential facts necessary to overcome the problems created by faulty positioning are to be understood.

In the great majority of cases, occipitoposterior positions undergo spontaneous anterior rotation followed by either a spontaneous or an easy low forceps delivery. Since spontaneous outcome is the rule in these cases, labor with the occiput posterior should be regarded as simply a variation of normal labor. The duration of the second stage is often slightly prolonged, however, because more work by the expulsive forces is required to effect rotation through the greater arc. In at least a third of the cases, moreover, rotation does not take place until the vertex reaches the pelvic floor. These facts should be recalled in the management of these labors, since additional time and patience are sometimes required if spontaneous rotation is to be achieved.

In a small proportion of cases, estimated by Calkins[6] to be about 5 per cent, rotation does not occur, and under such circumstances, the condition is referred to as persistent occipitoposterior position.

In a certain minority of cases of occipitoposterior position, the occiput rotates posteriorly and spontaneous delivery ensues in this position, that is with the face to the pubis. By taking these cases into consideration, it may be estimated that of all cases in which the initial position of the occiput was posterior at the onset of labor, only about 4 per cent require operative interference.

Management.—The management of posterior positions varies considerably. Most obstetricians are agreed that time should be allowed after completion of the first stage for rotation to occur under the influence of labor pains. The length of this period varies in different clinics and in different patients in the same clinic. A wait of 2 hours in the second stage is the time usually set for this expectant period. As a matter of fact, many competent obstetricians do not wait this long, feeling that early expert correction is perfectly safe, even though they admit that many of these heads probably would have rotated spontaneously, had they waited longer.

Folger[7] voiced the sentiment of this group with these remarks, "We feel that the time to rotate a posterior in the second stage has arrived when the head no longer descends with pains or retracts between pains. This is especially true in a multigravida who had normal labors with their prior deliveries when the occiput was anterior. . . . I cannot see the logic of prolonging any labor in which the fault lies with a faulty position of the baby. Positional dystocia is

one of the most frequent causes of prolonged labor. When one sees the ease with which a head will descend after being rotated, he will never subject the baby or mother to the forces necessary to accomplish delivery with the occiput posterior.''

It requires much judgment (acquired through experience) to decide when the point has been reached after which a further wait is inadvisable. The usual signs of maternal and fetal distress are taken into consideration. For the average obstetrical attendant, the management of the persistant occipitoposterior position continues to be a major problem fraught with many dangers. His time, judgment, and skill are frequently taxed, and from his point of view the situation is not only tiresome and tricky, but at times treacherous. He is aware of the possibility of such assorted pathologic conditions as uterine inertia; maternal exhaustion, hemorrhage, and shock; rupture of the uterus from internal version; severe forceps trauma to the maternal soft parts; necrosis of the bladder wall; and likewise such gross injuries to the baby as cerebral damage and Erb's paralysis. Fortunately today, in most communities and clinics, such cases are either voluntarily or by departmental rules placed in the hands of expert obstetricians with the result that the damage to the mother and infant is but little increased over that of normal occipitoanterior positions.

Those who take the calculated risk of waiting longer than the critical 2 hours, must be mindful of two important considerations. One is that serious intracranial damage may develop before any signs are discernible. Such a condition may be suspected if the uterine contractions are strong and frequent and rotation is not resulting. The second point is that prolonged hard labor pains might produce so much molding of the fetal head that anterior rotation, manually or with forceps, becomes difficult or impossible.

In some patients, indications for interference may arise before the cervix is completely dilated. If the cervix is almost completely dilated, and the fetal head is at or below the midpelvic plane, I feel that it is not poor obstetrics to incise the cervix under careful scrutiny after the method of Dührssen, and complete delivery if this is urgent for fetal or maternal indications or both. Sometimes this narrow rim of edematous cervix can be pushed out of the way without much difficulty or lasting damage. If the cervix is only 6 to 7 cm. dilated and delivery is urgent, I certainly would prefer the proper abdominal route.

The best type of operative procedure to be employed will depend on the experience and training of the operator, the type of pelvis, the degree of molding of the fetal head, and the size of the infant. If the head is considerably molded (as will often occur if patience has been exercised in allowing time for spontaneous rotation) delivery by forceps as an occiput posterior or occiput sacral will usually prove the least traumatic measure to both mother and child.

The same is true if the pelvis is anthropoid or android in type or shows midpelvic contraction. Moreover, if the operator's experience with manual or forceps rotation is meager, delivery of the posterior occiput as such is usually the safest procedure. The decision to deliver the head as a posterior or occiput sacral depends fundamentally on whether or not factors are present which threaten to make artificial rotation especially difficult. In order to ascertain whether such factors are present, some obstetricians attempt rotation gently, either by hand or by forceps, and, if it is easy, carry it out, but if a molded head is so wedged in the pelvis as to interfere with easy rotation, they deliver the infant from the occiput posterior position.

If delivery of the occiput as such is decided upon, a deep mediolateral episiotomy should be made and the forceps extraction performed slowly. Considerably more traction is often required than usual and this should be spread

over 15 or 20 minutes with ample rest periods between pulls. Because of the longer duration of the operation, the baby should be spared the narcosis which might occur from general anesthesia, and spinal or caudal anesthesia used.

If it is elected to carry out operative rotation of a persistent occiput posterior, several procedures are available, namely, manual rotation followed by forceps extraction, rotation, and delivery with the Kielland forceps, and the Scanzoni technique of forceps rotation and reapplication followed by forceps extraction.

There are two modifications of the original Scanzoni which are being used with increased frequency. Bill's maneuver, described by Arthur Bill[8] of Cleveland about 1931, has been used on occasions in our hospital (Table III). The real difference is that the head is rotated higher in the pelvis where there is more room and this can be done with greater freedom. This technique can be found in most standard textbooks of obstetrics.

TABLE III. METHODS OF ROTATION

Manual	192
Kielland	116
Scanzoni maneuver	43
Bill's maneuver	7

There is a method used by King[9] and his associates which appears to be different from Bill's maneuver only in that the first blade is not removed from the vagina while reapplication is carried out, but this blade is merely swept to the opposite side. They believe this to be more effective in preventing the fetal head from slipping back to its original position.

Internal podalic version and breech extraction are favored by some. If performed early, as was done by Bill[8] in 317 out of 500 cases, the risks are slight and the results are satisfactory if the operator is skilled and the proper conditions are present. Late in the second stage the procedure is difficult and the danger of rupture of the uterus is considerable.

This procedure was not used at any time in our 5 year series. The general feeling is that it is a procedure traumatic to mother and child and is done so seldom that one rarely has the opportunity to develop any type of proficiency in its performance.

Cesarean section was never used for the treatment of occipitoposterior, per se. When, however, this positional dystocia created a situation where insistence on vaginal delivery would be hazardous to mother and infant, cesarean section was used without hesitation (Table IV).

TABLE IV. INDICATIONS FOR CESAREAN SECTION IN OCCIPITOPOSTERIOR POSITION

Cephalopelvic disproportion		127
Multiparas*	6	
Primiparas†	65	
Elderly primiparas†	56	
Cervical dystocia		61
Uterine inertia, second degree		43
Fetal distress		20
Abruptio placentae		13
Toxemia		12
Placenta previa		5
Ruptured uterus		2
Hemorrhage from blood dyscrasia after 37 hours' labor in first stage		1

*Infants were 8 pounds, 13 ounces, or over in weight.

†Eighteen cases of primiparas were associated with fetal distress.

The figures in Table V are interesting because they show an increase in time over the normal anterior presentation, but not the great increase that one would expect on a service where so many of the posteriors are treated expectantly.

TABLE V. DURATION OF LABOR IN OCCIPITOPOSTERIOR POSITION

	FIRST STAGE	SECOND STAGE
Multiparas	9 hours, 57 minutes	45 minutes
Primiparas	19 hours, 8 minutes	1 hour, 57 minutes
Elderly primiparas	19 hours, 28 minutes	1 hour, 57 minutes

TABLE VI. METHODS OF DELIVERY IN ALL CASES

METHOD	MULTIPARAS		YOUNG PRIMIPARAS		ELDERLY PRIMIPARAS		TOTALS	
	NO.	%	NO.	%	NO.	%	NO.	%
Cesarean section	75	12.7	122	33.1	87	54.7	284	25.4
Forceps delivery as occiput posterior	170	28.8	95	25.7	25	15.6	290	25.9
Manual rotation	132	22.5	48	12.8	12	7.8	192	17.1
Forceps rotation	68	11.5	75	20.3	23	14.1	166	14.8
Spontaneous rotation	30	5.1	17	4.7	8	4.7	55	4.9
Spontaneous delivery as occiput posterior	115	19.5	13	3.4	5	3.1	133	11.8
Total	590	100.	370		160		1,120	

Analysis of Table VI reveals that one would expect as to the outcome of labor in occipitoposterior when divided among multiparas, young primiparas, and elderly primiparas. Insurmountable difficulties in vaginal delivery eventuating in cesarean section were most common in the case of the elderly primiparas. Manual rotation was carried out successfully on more occasions in the case of multiparas as contrasted with the elderly primiparas. Previous labors no doubt have a favorable effect in preparation of the pelvic soft parts for obstetrical manipulation. Forceps rotation on the other hand had to be resorted to more often in the case of the young primipara (Table VII). Spontaneous delivery as an occipitoposterior, as one would expect, is more common in the multiparas in whom adequacy of the pelvis is less of a problem.

TABLE VII. COMPLICATIONS ASSOCIATED WITH FORCEPS ROTATIONS

Vaginal lacerations:	
First degree	8
Second degree	28
Third degree	8
Cervical lacerations	15
Intrapartum hemorrhage	15
Postpartum hemorrhage	15

Although our neonatal mortality rate was only 1 per cent, we are still much concerned about the 2 cases of prolonged labor and the poor fetal result (Table VIII). This emphasizes again the importance of the statement that expectant treatment is satisfactory as long as you know what you are expecting.

TABLE VIII. CAUSES OF 12 NEONATAL DEATHS

Cesarean section for fetal distress, term: Atelectasis	2
Prematurity, less than 31 weeks	8
Prolonged labor, 48 hours, subdural hematoma	2

Comment

Proper management of occipitoposterior begins in the first stage. We also feel that the difficulties in the second stage are proportionate to neglect in the first stage. We recommend awaiting spontaneous rotation, but recommend interference at the end of 2 hours. This allows nature to do her work when she can, and, when she is incompetent, we recommend interference at a time when interference can be done easily, before molding of the head and contraction bring dystocia and increase the difficulty.

The head in occipitoposterior position as a rule is a bit deflected; therefore, when grasped for the purpose of rotation, pressure should be exerted on the forehead to favor flexion. Pressure on the shoulder with the assisting abdominal hands is of great assistance in completing the rotation.

If manual rotation is unsuccessful, an attempt at forceps rotation should be made. If this fails, resort to cesarean section should be made before the mother is unalterably traumatized or the baby significantly compromised.

We do not consider labor to be an endurance test between mother, baby, and doctor. We feel that active intervention is sometimes more conservative than a "wait and see" attitude. Dieckmann[10] was correct in saying that it is all right to watch a patient if you are watching for something and are prepared to recognize when this is accomplished. Failure of progress after the cervix is fully dilated should be explained.

When prolongation of labor is due to fetopelvic disproportion, the operator must judge not only when conditions warrant interference but also the type of interference best suited to good maternal and fetal results. In this group the art of obstetrics dominates technique for here it comprises a systematic application of knowledge and skill for the production of the most highly desired end results. There is no one way of best managing any of the cases of prolonged labor due to fetopelvic disproportion; there is only a best way for each one.

With positional dystocia as in occipitoposterior, the resolution of prolonged labor rests upon accurate examination and the decision that it alone is the cause. One might correct the position and deliver vaginally with ease most patients with positional dystocias since after correction there are rarely any difficult forceps deliveries in normal pelves. On the other hand, to insist, after a correction of the malposition, on a vaginal delivery through a pelvis contracted relative to the given fetus is to gamble away the mother's tissues, if not her life, and the fetal bones and brains.

If the attending physician is baffled, he should secure competent assistance long before the patient is exhausted, the maternal soft parts damaged, and the baby mutilated. Give the consultant, the mother, and the baby a fair chance.

We wish to express our gratitude to Dr. A. M. McCarthy and Dr. Frank Schade for their constructive criticisms and helpful suggestions.

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THE USE OF GLUTETHIMIDE* IN THE LABOR PATIENT†

A Report of 50 Cases

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EARLIER investigators have shown glutethimide to be a useful sedative in several branches of medicine.[1-4] The purpose of this study was to determine the effectiveness of glutethimide as a sedative in early labor, and its usefulness as a synergist in reducing the requisite amount of concomitant analgetic. This study was calculated to contribute answers to the following questions:

1. Is glutethimide an effective sedative in the first stage of labor?
2. Will glutethimide have a synergistic effect with meperidine?
3. What will be the result of this combination on fetal respiration at the time of delivery and immediately post partum?

Method and Materials

The study consists of 75 patients between the ages of 16 and 36 years admitted to the Obstetrical Service of the City of Memphis Hospitals, Memphis, Tennessee. All were evaluated on admission to be normal labor patients with no known or anticipated complications. The group included 23 primigravidas, 11 secundigravidas, and 41 multigravidas with an average gravidity of vi.

Each patient was evaluated prior to the initial dosage of glutethimide for vital signs and for physical and emotional status in order to establish a base line for later comparison. An initial dose of 1 Gm. orally was given to each patient when labor was ascertained to be active and she was then followed closely throughout her entire course of labor with interval evaluation. Particular attention was paid to fetal respiration at the time of delivery and immediately post partum. Meperidine was given parenterally after evaluation of glutethimide; it was given when needed, in 50 mg. doses, to maintain a smooth course of labor.

The study group (50 patients) was compared with 25 patients who differed in that they received oral secobarbital sodium rather than glutethimide, that is, a ratio of 1 Gm. of glutethimide to 200 mg. secobarbital sodium. In this control series secobarbital sodium was given initially only.

Evaluation

To classify the effects of glutethimide alone, each patient (prior to any analgesia) was evaluated objectively during labor and placed in one of the

*Doriden, Ciba Pharmaceutical Products, Inc., Summit, N. J.

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following groups: An excellent response was recorded for a patient with diminished reactions to pain during contractions who slept between. A patient who was observed to be restless during contractions but sleeping between was classified as having had good results. The patient was considered to have had a fair response when she was restless during contractions with more relaxation between. The patient's responses were recorded as poor (noneffective sedation) when she was restless both during and between contractions.

At the time of delivery the fetus was evaluated and classified in accordance with the following criteria: Any infant who displayed an immediate cry with normal respiration within 1 minute after delivery and was of normal pink coloration was placed in classification I. An infant who was observed to have a weak cry and/or dusky coloration with normal respiration established within 3 minutes was placed in classification II. Classification III included those infants with a delayed cry and respiration and/or cyanotic appearance with response to routine resuscitation. A cyanotic infant who required serious efforts for resuscitation was designated IV. The infants in classifications III and IV were considered depressed.

Observations

No adverse side effects were noted which could be attributed to glutethimide. Blood pressure and pulse fluctuated throughout labor within the limits of normal and the respiratory rate varied little.

The average duration of labor was 4 hours with the range from 16 hours and 53 minutes to 1 hour and 30 minutes. There developed, during the course of labor, 3 cases of occiput posterior, resolved by manual rotation and spontaneous delivery, and one case of transverse arrest, resolved by forceps rotation and delivery. Secondary uterine inertia occurred in 3 cases terminated successfully after rest, hydration, and Pitocin stimulation via intravenous drip. It is interesting to note that in these complicated cases in which labor was of longer duration and in which the dosages of glutethimide and meperidine were increased above average, the infants were delivered in excellent condition with the exception of one, who was easily resuscitated.

The types of delivery and anesthetics used in this study are summarized in Table I.

TABLE I. CHOICE OF DELIVERY AND ANESTHETIC UTILIZED

	ANESTHETIC			
TYPE DELIVERY	NONE	NITROUS OXIDE AND OXYGEN	SADDLE BLOCK	PUDENDAL BLOCK
Spontaneous	5	38	2	4
Low forceps	0	0	25	1

Results

The results of the comparative study of glutethimide and secobarbital sedatives during the first stage of labor are summarized in Table II. The sedation during labor of 5 patients who received glutethimide was classified as excellent, of 25 as good, and of 12 as fair; therefore, glutethimide was considered to be an effective sedative in 84 per cent of the patients studied. Eight of the group, or 16 per cent, derived no positive effect from glutethimide. Secobarbital was equally effective as a sedative and the same percentage of noneffective sedation was apparent.

TABLE II. EFFICACY OF DRUGS

DRUG	NO. OF PATIENTS	CLASSIFICATION			
		EXCELLENT	GOOD	FAIR	POOR
Glutethimide	50	5	25	12	8
Secobarbital	25	2	14	5	4

The criteria used indicate that the drugs were equally effective sedatives in early labor except for the slight difference in the time required for onset. The average period before initial onset of effect was 24.7 minutes for glutethimide and 30.5 minutes for secobarbital sodium.

Twenty-nine of the glutethimide patients were carried through labor on 50 mg. of meperidine, as were 8 patients who received secobarbital. Eleven patients in each group received 100 mg. of meperidine. Four patients who received glutethimide and 5 who received secobarbital required more than 150 mg. of meperidine. Meperidine was not required in one patient who was given secobarbital and 6 patients were carried on glutethimide alone. Two of the latter 6 received no analgetic by choice and the other 4 were delivered rapidly following spontaneous rupture of the membranes.

TABLE III. TOTAL MEPERIDINE DOSAGES

	MG. MEPERIDINE			
	0	50	100	150 OR MORE
Glutethimide	6	29	11	4
Secobarbital	1	8	11	5

It can be seen from Table III that 92 per cent of the patients who received glutethimide went through labor on a total of 100 mg. of meperidine or less and 70 per cent went through labor on 50 mg. or less. In contrast, only 80 per cent of the patients who received secobarbital went through labor on 100 mg. of meperidine and 36 per cent went through labor on 50 mg. or less.

TABLE IV. AVERAGE AMOUNT OF ANALGETIC RECEIVED PER HOUR

	HOURS OF LABOR	MG. MEPERIDINE	MG. MEPERIDINE/HOUR
Glutethimide	200	3,150	16
Secorbarbital	75	2,175	29

Table IV shows that approximately half the amount of meperidine per hour of labor was required when the patients were given glutethimide rather than secobarbital for sedation. The potential of glutethimide as a synergist with meperidine is indicated by this series and warrants further study.

TABLE V. FETAL DEPRESSION

DRUG (MEPERIDINE GIVEN IN BOTH SERIES AS A COMMON ANALGETIC)	NO. OF PATIENTS	CLASSIFICATION			
		I	II	III	IV
Glutethimide	50	32	12	5	1
Secobarbital	25	11	7	3	4

The data on fetal depression are summarized in Table V. It can be readily seen that the incidence of fetal depression was more than twice as great in the secobarbital group.

The mother of the only infant classed IV in the glutethimide study had an excellent course of labor. She received a total of 1 Gm. of glutethimide and 50 mg. of intravenous meperidine one hour and 15 minutes before being delivered by low forceps and episiotomy with the use of a saddle block.

TABLE VI. TIME INTERVAL FROM LAST GLUTETHIMIDE DOSE TO DELIVERY

TIME INTERVAL (HOURS)	NO. OF PATIENTS
0-1	5
1-2	21
2-3	12
3-4	6
4-5	3
5	3

The interval between the last dose of glutethimide given prior to delivery and the delivery itself is given in Table VI. The wide time range tends to bring out any relationship between time of dose and effect of sedation on the infant's respiratory action. It appears, however, that no correlation can be made in this small series.

Summary

1. Glutethimide has been evaluated as a sedative in 50 normal labor patients, and its sedative value compared with results obtained in 25 patients in whom secobarbital sedation was used.

2. Eighty-four per cent of the patients in each of the drug groups displayed objective sedation.

3. The average delay in onset of the sedative effect was found to be 24.7 minutes for glutethimide and 30.5 minutes for secobarbital.

4. Ninety-two per cent of the labor patients who received sedation with glutethimide and 80 per cent of those with secobarbital went through labor on 100 mg. or less of meperidine; 70 per cent of the glutethimide-treated patients and 36 per cent of the secobarbital-treated patients progressed through labor on 50 mg. of meperidine or less.

5. Approximately twice as much meperidine per hour of labor was required for the secobarbital group.

6. There was no apparent correlation between fetal depression and the time of the last dose of glutethimide.

7. The incidence of fetal depression was 12 per cent in the glutethimide series of 50 patients and 28 per cent in the secobarbital group of 25 patients.

8. Glutethimide was found to be essentially free from adverse side effects.

Conclusion

Glutethimide, in the dosages used, is concluded to be a safe, satisfactory hypnotic which induces ample sedation in the normal labor patient and which compares favorably in potency with 3 grains of secobarbital sodium. There is an indication from this series of 50 labor patients that when glutethimide and meperidine are used in combination, approximately half as much meperidine

is needed to maintain a smooth course of labor as is needed when meperidine is given in combination with secobarbital. In what appears to be a direct relationship, the incidence of fetal depression was more than twice as great in the secobarbital group. Additional study is warranted to further substantiate these findings.

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DYSTOCIA CAUSED BY WILMS'S TUMOR

With Case Report

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DYSTOCIA caused by fetal abdominal swelling is not often encountered. It may be caused by polycystic kidney, renal hypertrophy, urinary retention, idiopathic ascites, hydrops fetalis, and neoplasms. Of the neoplasms which cause dystocia, Wilms's tumor occurs rarely. In a review of the literature, very few cases recognized at birth were found. Even rarer are the cases which caused dystocia.

Josephs,[1] Brogan,[2] and Silver[3] have reported cases of Wilms's tumor with dystocia. Porter and Carter[4] reported a case of sarcoma in a full-term infant causing dystocia, and mentioned that sarcomas have been found in the kidney as early as the sixth fetal month. Ahari and Michael[5] reported a Wilms's tumor in a 5-week-old infant. Hartenstein[6] and Nicholson[7] have reported cases in newborn infants but there was no associated dystocia. In reviewing the literature Hartenstein[6] found 6 additional cases of "malignant renal neoplasms occurring in premature or full term stillborn or in older infants with symptoms or signs of the neoplasm since birth." In 1897 Walker[8] reviewed the literature and found 2 cases of embryonal sarcoma in 7 months' fetuses. He also found 8 cases of these tumors which were noticed at birth. In 1932 Dean and Pack[9] found one additional case of embryonal renal adenosarcoma in a 7 months' fetus. They also found 3 additional cases of the tumor in newborn infants. In Campbell's[10] *Urology,* he refers to a case of Wilms's tumor in a 3-day-old infant. Lowsley and Kirwin[11] also refer to such a tumor as having been "observed in the newborn infant and even in an 8 months fetus (Cutler and Buschke)." Of the neoplasms which occur during the first 10 years of life, it is second in frequency only to those of the orbit and the eye.[12] Wilms's tumor has been referred to as embryonic renal tumor, renal sarcoma in infancy, embryonal adenomyosarcoma, adenomyofibrosarcoma, adenosarcoma, nephroblastoma, mixed tumor, myosarcoma striocellulare, rhabdomyosarcoma, embryonic sarcoma, and malignant embryonal adenocarcinosarcoma. It is an embryoma of the kidney and is highly malignant.

Many theories have been conceived as to its origin. Some of these theoretical sources are: (1) aberrant germ plasm, (2) Wolffian body rests, (3) renal blastema. Boyd[13] felt "that the occasional formation of muscle and cartilage is a perversion of growth on the part of the embryonic mesenchymal cells." Nicholson[7] thought that the tumors are developmental malformations: "They represent the physiological evolution of a somatic tissue after abnormal stimulation at a time when growth is active and differentiation begins. The tumor does not arise in a malformed organ but represents, and is, the malformed organ."

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In a child an abdominal mass is usually palpated by the mother or by the doctor during a routine examination. There may be abdominal pain. Hematuria usually occurs late in the course of the disease as well as vomiting, anorexia, weight loss, malaise and fever.

The intravenous pyelogram is the most helpful test in the diagnosis. If this is unsatisfactory, then retrograde pyelography may be done. The patient's age must be considered in the latter case. Transillumination may help to differentiate a tumor and a cystic mass. Needle biopsy may also be performed, but dissemination of tumor cells must be considered prior to its use. An abdominal flat plate may also aid in the diagnosis.

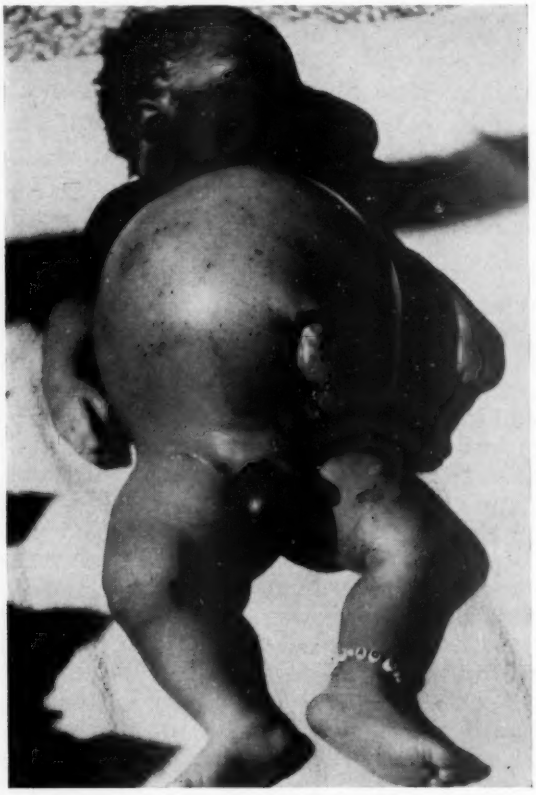

Fig. 1.

A 32-year-old Negro woman, gravida ix, para vii (children aged 1 to 10 years), was first seen for prenatal care in our clinic on July 15, 1957. She had had one miscarriage in 1955; the condition at birth of her other babies had been good. Her last normal menstrual period was Jan. 28, 1957, and the estimated date of confinement was Nov. 4, 1957.

The initial physical examination showed a very obese patient (271 pounds) with a height of 5 feet, 7 inches. The blood pressure was 104/70. The fundus measured 31 cm. above the symphysis pubis. The pelvic examination disclosed no abnormal findings from those of a grand multipara in the last trimester of pregnancy. The fetal heart tones were heard in the right lower quadrant of the abdomen, and the presentation was a vertex. The rest of the physical examination was not remarkable except for obesity.

Initial laboratory work was as follows: Urinalysis, 4 plus pus; hemoglobin, 10.7 Gm.; leukocyte count 13,050 with 78 polymorphonuclear cells and 22 lymphocytes; the Rh factor was positive; blood VDRL test was negative.

The anemia and pyuria were treated, and she was instructed about weight control. During the first week after examination, she gained ½ pound. On her return visit one week later, July 29, 1957, she had lost 6½ pounds. On her next visit, Aug. 13, 1957, she had gained 22 pounds (weight 287 pounds) and had a 3 plus pitting pretibial edema. At this time the blood pressure was 120/86, and the urine contained a few pus cells. She was given a prescription for an oral diuretic and again instructed regarding diet limitation. Her weight 2 weeks later, Aug. 28, 1957, was 300 pounds, a gain of 13 pounds. This patient gained 29 pounds during the 6 weeks of care.

She was admitted to the hospital on Aug. 28, 1957, and placed on a pre-eclampsia regimen. Blood chemistry determinations on admission showed blood urea nitrogen 9.0 mg., uric acid 11.2 mg., and creatinine 1.7 mg. Five days later the blood urea nitrogen was 11.2 mg. The blood pressure varied from a high of 146/96 to a low of 120/80. Her weight decreased to 250 pounds by Sept. 6, 1957.

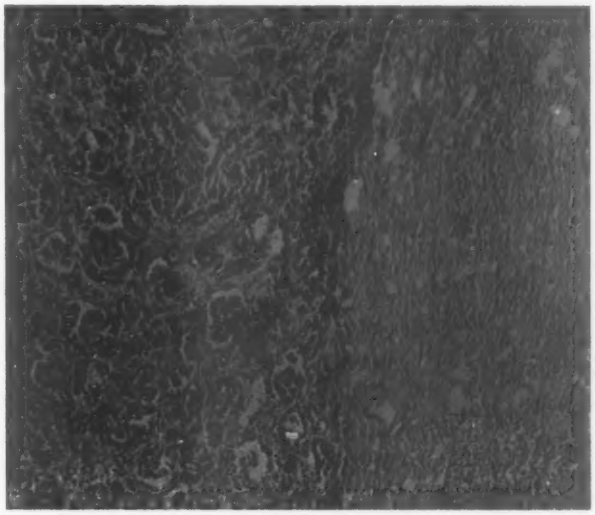

Fig. 2.

Five days after admission she went into spontaneous labor. The fetal heart sounds were heard in the right lower quadrant at a rate of 136 per minute and were of good quality. Labor progressed satisfactorily and after 2 hours of labor the cervix was 6 cm. dilated and the station was plus 1. She was then taken to the delivery room where a sterile vaginal examination showed a vertex presentation in a left occipitoanterior position. After the cervix was fully dilated and the station was plus 2, she was anesthetized with open drop ether. The membranes were ruptured artificially, and the head was delivered spontaneously without difficulty from a left occipitoanterior position. There was much difficulty rotating and delivering the shoulders. A right mediolateral episiotomy was performed but delivery did not progress. An attempt was made to fracture the clavicles in order to facilitate delivery but this was unsuccessful. It was discovered at this time, by palpation, that the infant's abdomen was grossly distended and enlarged. After 15 minutes of traction on the head with an assistant exerting fundal pressure through the abdomen, the baby was finally delivered. The cord was then clamped and tied. The placenta was delivered immediately and was very large and intact with the membranes. The estimated blood loss was 300 c.c. The first stage of labor lasted 2 hours and 15 minutes, the second stage 40 minutes, and the third stage 3 minutes.

The infant's heart was beating after delivery, and there were shallow respiratory movements present. No breath sounds were heard. The pharynx was suctioned with a bulb syringe. After an unobstructed airway was obtained, positive pressure oxygen was

given with an E & J resuscitator but the lungs could not be expanded because of the abdominal pressure. A Levin tube was passed into the stomach but no gastric contents were obtained. Paracentesis was then done and only a few cubic centimeters of thick, dark-red, bloody fluid was obtained. After 30 minutes the heart ceased beating.

Fig. 3.

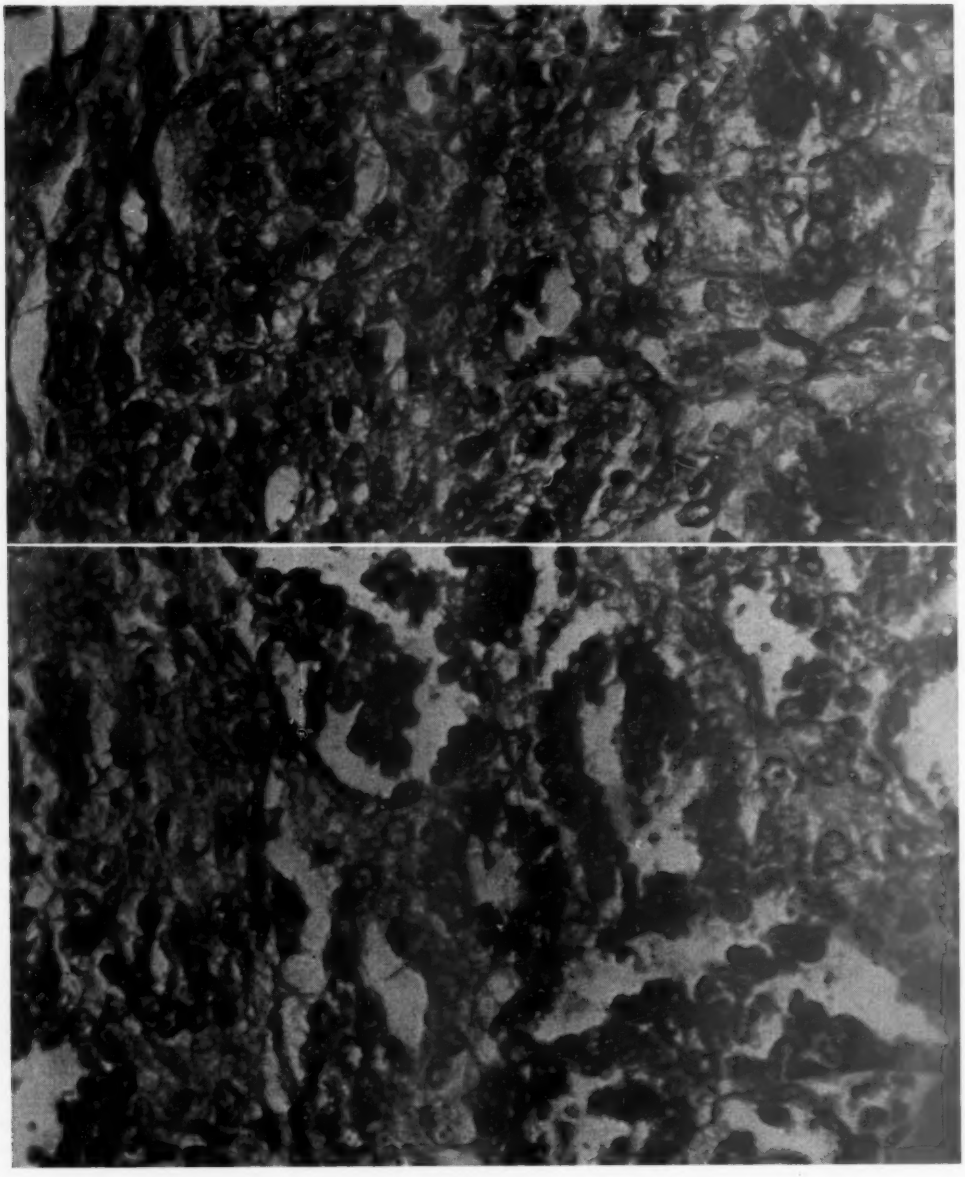

Fig. 4.

The baby was a male with a weight of 9 pounds, 14 ounces, and a length of 19 inches. The abdomen was tremendous, as shown in Fig. 1. It measured 19 inches in circumference. The scrotum, penis, face, and eyelids were markedly edematous. No abdominal mass was palpable although there was increased density on the right side.

Permission for autopsy was obtained and the significant findings were limited to the abdominal cavity. There was 50 c.c. of serosanguineous fluid free in the peritoneal cavity.

The liver was displaced to the left by a retroperitoneal mass measuring 12 by 11 by 6.5 cm. occupying the right kidney area. The mass had a homogeneous gray appearance and was slightly soft. There was a serosal membrane covering the entire mass except for a few loops of intestine. Attached to the anterior central portion of the tumor were the cecum and appendix. This tumor mass weighed 400 grams when removed.

On cut section the outer 3 cm. of the tumor consisted of rather firm, pale, pink-to-tan tumorlike tissue. In the more central portion, extending to the periphery, half of the tumor mass was friable and between pieces of tumor there was caseous, necrotic material. The capsule was a thin-walled connective-tissue layer and did not peel easily from the surface. Surrounding the mass in adjacent tissue, there was a layer of blood and edematous tissue 3 to 4 mm. thick.

The right kidney was identified on the posterior aspect of the tumor and measured 5 by 3 cm. The depth of the kidney was only 4 mm. The pelvis on the right was markedly dilated and the ureter was 1 cm. in circumference. There seemed to be a very thin capsular membrane separating the right kidney from the tumor mass, as shown in microscopic section (Fig. 2). The left kidney measured 6 by 2.5 by 1.5 cm. and showed marked pyramid formation.

The lungs had not been aerated and were solid. The rest of the autopsy findings were essentially normal.

Microscopic examination showed the tumor mass to be composed of two distinct types of cells. One type, apparently nonepithelial, formed the stroma and constituted about 25 per cent of the tumor mass, as seen in Fig. 3. The other type was apparently epithelial and formed tubular structures mimicking moderately closely the renal tubules of the ordinary infant kidney, as seen in Fig. 4. These might be seen in all stages from solid sheets to well-developed tubular structures. There were also proglomeruli in various stages of development although no completely developed glomeruli were present. The cells of the stroma were poorly differentiated so that only an occasional group of cells which resembled adult fibroblast or smooth-muscle cells were seen.

The final anatomical diagnoses were: (1) Wilms's tumor of the right kidney and (2) fetal atelectasis.

Summary

1. Dystocia resulting from abdominal swelling in the fetus is rare.

2. Wilms's tumor of the kidney is one of the neoplasms which sometimes causes dystocia.

3. The available English literature concerning this tumor in the fetus and newborn has been summarized.

4. A Wilms's tumor in a fetus causing dystocia at delivery has been presented.

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INTERLOCKED TWINS

Report of a Case of Chin-to-Chin Locking

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THE complication of interlocked twins of all types is extremely rare. According to Von Braun, as quoted by Friedman[1] and Kimball and Rand,[4] the incidence is one in 90,000 deliveries. Because of its rarity the following case of chin-to-chin interlocking is reported.

Mrs. J. C., aged 24 years, a white primigravida approximately 34 weeks pregnant, was admitted to the hospital at 9:30 A.M., Aug. 9, 1955. The patient had been in labor for 2 hours and the membranes had ruptured just prior to admission. Her prenatal course was not remarkable. Physical examination on admission disclosed a blood pressure of 104/70 and 1 plus bilateral ankle edema. The uterus was enlarged to 7 fingerbreadths above the umbilicus and contractions were of good quality occurring every 5 minutes. The fetal heartbeat was 128 and regular in the left lower quadrant. Rectal examination showed the cervix to be well effaced and dilated 4 cm., with a frank breech presenting at minus 2 station. Pelvimetry (Colcher-Sussman) taken an hour after admission showed twins and an adequate pelvis (Fig. 1). Twin A presented as a breech in right sacroanterior position and twin B as a vertex floating above the pelvic brim on the left. The conclusion by the radiologist was: "Twin pregnancy, breech presenting, cephalic to follow. No roentgen evidence of cephalopelvic disproportion." Routine laboratory findings on admission were not remarkable.

Labor progressed without incident to full dilatation in 14 hours. After 45 minutes in the second stage the patient was brought to the delivery room. The fetal heart rates were 128 in the left lower quadrant and 132 in the right lower quadrant, both of good quality and regular. Twin A presented as a frank breech at the introitus and at that time intact presenting membranes were ruptured artificially. Clear amniotic fluid was obtained. Under gas anesthesia an episiotomy was made and a breech extraction of a frank breech was accomplished without difficulty up to the point of delivering the aftercoming head. Pelvic examination at that time showed the head of twin B to be engaged in the right occiput posterior position. The neck of twin A was pressed forward against the symphysis and the vertex was above the pelvic inlet (Fig. 2). Attempts to disengage the chin-to-chin interlocking by rotation and upward displacement of vertex B were not successful. Simpson forceps were applied to the vertex of twin B and traction for a test of delivery was not effective. Approximately 5 minutes from the start of the breech extraction the heart of twin A became inaudible. The heart of twin B was irregular in rhythm and barely audible. Traction was applied to the shoulders of twin A and decapitation was accomplished by utilizing an episiotomy scissors. With fundal pressure twin B was delivered easily within the following minute. The amniotic sac of twin B was already ruptured which presumably accounted for the leakage of amniotic fluid during early labor. The vertex of twin A was then removed manually as was also a fused placenta demonstrating two cords. The placenta

and membranes were intact. Exploration of the uterus showed no abnormalities and intramuscular ergotrate was then given to the patient. No lacerations were found on examination of the cervix and vagina, and the episiotomy was then repaired. The total blood loss was estimated at 250 c.c. Twin B weighed 2,375 grams and was in good condition following mouth suction and the administration of oxygen. Twin A weighed approximately 1,800 grams.

Following an uncomplicated postpartum course, the mother was discharged alone on the fifth postpartum day. Twin B was discharged well from the pediatric service approximately 10 days later, weighing 2,390 grams. A subsequent pregnancy was terminated without incident in July, 1957.

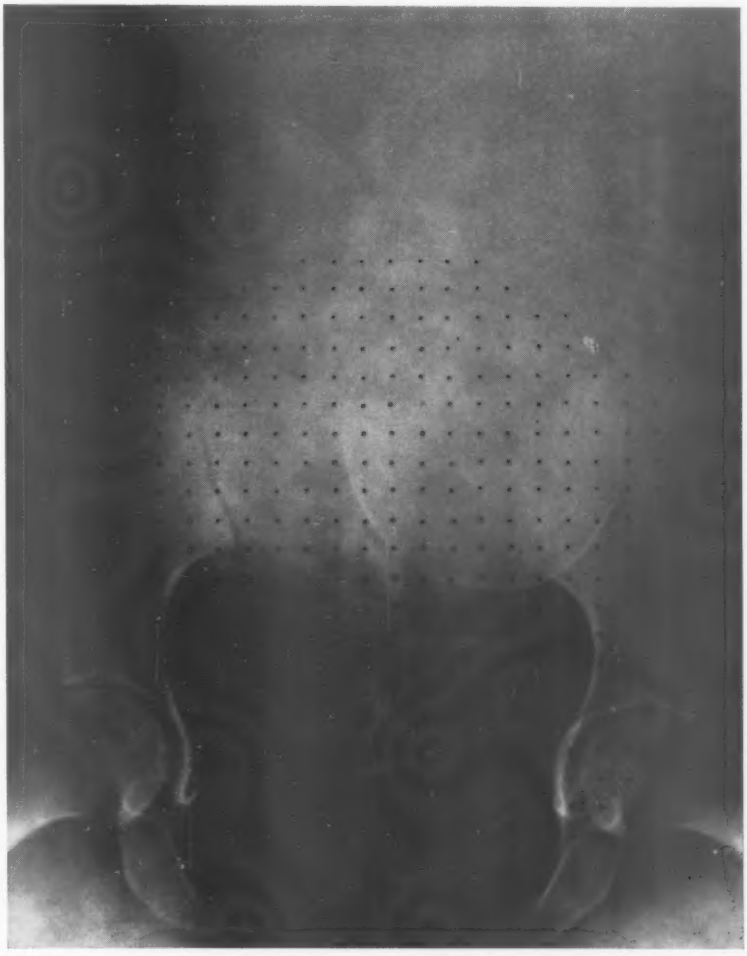

Fig. 1.—Anteroposterior view showing twin A presenting as a breech in right sacroanterior position and twin B as a vertex floating above the pelvic brim.

Comment

Primiparity, unusual positions in utero, and deficiency in amniotic fluid in both amniotic sacs are believed to be predisposing causes for this complication.[1]

The exact type of interlocking depends upon the positions of the twins. When the first fetus presents as a breech and the second engages simultaneously as a vertex, then chin-to-chin interlocking may result. Two vertices or two

breeches entering the pelvis simultaneously may also interlock. If one twin is in a transverse lie, interlocking may occur when the other twin engages. In order to produce chin-to-chin interlocking, however, the uterine contractions must be strong enough to force the vertex of twin B into the pelvis simultaneously with the presenting breech and the pelvic measurements great enough to permit this. If the pelvic inlet measurements are borderline, simultaneous engagement of vertex and breech is unlikely unless the babies are extremely small. There may be a deficiency of amniotic fluid due to oligohydramnios or early rupture of the membranes.[2]

Fig. 2.—Chin-to-chin interlocking of twins. (From Beck and Rosenthal: Obstetrical Practice, ed. 6, Baltimore, 1955, Williams & Wilkins Company.)

The management of interlocked twins depends upon the type of interlocking as well as the stage of labor at which the complication is discovered. Cesarean section is the best mode of delivery when the diagnosis is made by x-ray in early labor while the fetuses are viable.[3] If the diagnosis is not made until the delivery procedure has begun, management again will depend upon the type and extent of interlocking. With chin-to-chin interlocking that develops while twin A is being delivered as a breech, an attempt is made initially to rotate manually and to displace the second vertex upward. If this procedure is not successful then the maneuver described by Kimball and Rand[4] should be tried. In this maneuver, Piper forceps are applied to the vertex of twin B, and by gentle steady traction twin B is delivered first. If there is unusually strong resistance, however, this procedure should be discontinued and must be considered a failed forceps. If the above attempts to disengage the twins fail, then decapitation of twin A and vaginal delivery of twin B should be accomplished as expeditiously as possible.[5] In all other types of interlocking discovered late in labor, attempts are first made to unlock the twins vaginally. If they cannot be separated easily then cesarean section should be done.

Pelvimetry taken prior to labor or during early labor is helpful in discovering this complication. The earlier the diagnosis, the more favorable the result. Chin-to-chin interlocking may possibly be prevented if an assistant can hold the vertex of the second twin abdominally while the breech is being delivered. When possible this should be augmented by upward pressure on vertex B through

the vagina while breech A is being extracted. Finally, fundal pressure must be avoided during the delivery of twin A since this may precipitate the complication.

Summary

1. Chin-to-chin interlocking is a rare complication of the delivery of twins, occurring once in 90,000 cases.

2. Primiparity, unusual positions in utero, and deficiency in amniotic fluid in both amniotic sacs are believed to be predisposing factors. Premature rupture of the amniotic sac of twin B as in the case reported may also be a predisposing factor.

3. The detection of the possibility of this complication before the delivery procedure is begun usually permits prevention or satisfactory resolution of the problem.

4. Cesarean section is the best mode of delivery when the diagnosis is made by x-ray prior to or during labor while the fetuses are viable. If the diagnosis is not made until the delivery procedure is begun then manual rotation and upward displacement of vertex B are attempted. If these measures fail, then the maneuver described by Kimball and Rand utilizing Piper forceps on vertex B should be attempted. If all attempts to unlock the twins fail then destructive operation is the only remaining course of action.

5. A case of chin-to-chin interlocking of twins is reported. The management of interlocked twins is reviewed.

We are grateful to Dr. Clayton S. Hitchins for his assistance.

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LABOR FOLLOWING SEVERE THERMAL BURNS

A Case Report

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OUR present-day medical literature is replete with reports of the changing concepts in the pathology and treatment of burns. Little space, if any, however, has been given to the management of the pregnant victim of burns. It is possible that today's obstetrician will be faced with the problem of maternal and fetal salvage should a major thermal disaster befall modern civilization. Therefore, a brief review of our knowledge of endocrine function in burns and labor may help to stimulate speculation on the presented case.

Endocrine Function in Burns and Labor

A significant number of burn victims die without demonstrable gross or microscopic evidence to explain the cause of death. A continuous search for a lethal toxin or toxins which may be emitted into the blood stream from the burned area has, to date, been unrevealing. Roos, Weisiger, and Moritz[12] in their study proposed two possible mechanisms for the cause of deaths from burns: first, the heat may raise the temperature of the blood to a point where irreversible fatal thermal changes occur in the brain and heart; second, a release of potassium to levels as high as 11 to 13 mg. per liter may cause cardiac standstill and death.

Weiskotten,[17] who investigated the pathologic anatomy of burns, concluded that the most profound and specific changes occur in the adrenal glands. He observed an increase in weight from a normal 4 to 7 grams to 20 to 25 grams. Enlargement occurred in the adrenal cortex with individual cells undergoing hypertrophy associated with a loss of their lipid granules. In his description of the general adaptation syndrome, Selye[13] noted similar changes in the adrenals following a variety of stressful situations. He pointed out that the adrenal medulla undergoes a conversion with the discharge of chromaffin granules and vacuolization of the cells. These morphologic changes, accompanied by an increased output of the adrenal hormones, begin almost immediately and reach a peak in about 48 hours. When the subject recovers these variations are reversible.

The cause of initiation of the coordinated activity of the uterus in labor remains in the realm of theory. Research, however, has confirmed the existence of an intrinsic nervous mechanism in the uterus,[7] not resembling any cell or group of nerve cells in the body. Studies and experiments on the pregnant uterus before and during labor are in progress for the purpose of clarifying the action of hormones on the uterine muscle.

During pregnancy the appearance of acidophilic cells, called pregnancy cells, causes the anterior pituitary lobe to enlarge to about twice its normal size. It has been stated by Soffer[14] that during gestation the pituitary gland has little or no gonadotrophic but a tendency toward increased lactogenic activity. Chemical and pharmacologic studies on the posterior pituitary lobe have illustrated that this section of the gland can initiate uterine contractions by the action of the hormones oxytocin and vasopressin. The vasopressin fraction contains the antidiuretic hormone. A mean rise in the antidiuretic substance during the menstrual cycle and a higher level during pregnancy was observed by Hawker.[2] Page[10] suggested that the increased pitocinase activity of plasma during gestation may indicate hyperactivity of the posterior pituitary gland. Such a mechanism may serve to prevent the stimulating action of oxytocin on the uterus, while the sudden disappearance of the substance at term will result in the onset of labor.

Normal function of the ovary is maintained until the placenta takes over the secretion of estrogen and progesterone. After this conversion the entire ovary may be removed without altering the outcome of the pregnancy.

The adrenal glands, particularly the adrenal cortex, hypertrophy during the later part of pregnancy and recede after delivery. Venning[16] found the rise in adrenal steroids to be to about four times their normal value during the last trimester and especially at delivery, this coinciding with the peak excretion of gonadotrophin. Gemzell[1] illustrated that this peak falls to below normal within 6 days after delivery. In analyzing placental extract, Pearlman,[11] and later Johnson and Haines[4] demonstrated the presence of adrenal cortical hormones. This supports the observation of Hench[3] that patients suffering from rheumatoid arthritis find relief during pregnancy, and that of Knowlton,[5] who noted temporary improvement of Addisonian disease throughout gestation. The amount secreted from the placenta, however, is thought to be insufficient to act as a solitary stimulus on the pituitary gland. Landesman[6] testified to an increased sensitivity to epinephrine during pregnancy, rising at the time of labor. This diminishes during the first postpartum week.

Enlargement of the thyroid gland in early pregnancy is interpreted as indicative of an increase in the growth hormone. Labor is unaffected.

Newman,[9] and Spingarn and Geist,[15] contributing to the knowledge of serum electrolytes and the parathyroid hormones during normal pregnancy, found that the serum calcium and phosphorus decrease slightly from the twenty-fourth to the twenty-eighth week, rising toward the time of delivery. The serum potassium remains within normal limits throughout the pregnancy.

Case Report

A 23-year-old white woman, gravida ii, para i, was transferred to the Bernalillo County-Indian Hospital on Oct. 11, 1957, 2 days after being burned in a butane gas explosion in her trailer home. Before her transfer she received emergency treatment, consisting of intravenous fluids, 100 mg. of Demerol every 3 hours, and dressing of the burned areas.

On admission the physical examination was essentially negative except for the burns. These covered 50 per cent of the total body surface and were located on the face, both upper extremities, the entire back, and both legs. The abdomen was soft and the uterus enlarged, the fundus rising approximately 27 cm. above the symphysis pubis. Gestation was estimated at about 7½ months. Uterine contractions, lasting from 30 to 40 seconds, were palpated at 4 to 5 minute intervals. A vaginal examination showed that the cervix was 2 cm. dilated and 50 per cent effaced. The amniotic membranes were bulging.

The surgical service continued administration of 100 mg. of Demerol every 3 hours, along with levallorphan tartrate* to counteract the narcotic effect on the fetus. Releasin,† 4 c.c. in 500 c.c. of normal saline, was given intravenously, followed by 1 c.c. intramuscularly every 4 hours. Although uterine contractions subsided, the patient was spontaneously delivered of a living 4 pound, 9 ounce female infant on October 14. On October 25, a débridement of the upper extremities was performed. The patient died the following month.

The newborn infant was immediately placed in an Isolette. Within 30 minutes after delivery, she developed cyanosis and sternal retraction. Roentgen examination suggested hyaline membrane disease. She was successfully treated by the pediatric service and was discharged on November 8, after a weight gain of 1 pound.

Comment

This patient was treated primarily for burns and shock. Forty-eight hours later she went spontaneously into labor, attempts to prevent it having failed.

It has been observed that shock following burns or other physical trauma,[8] such as central nervous system injuries and fractures of bones, does not necessarily act as an immediate stimulus to the pregnant uterus. The toxin of burns liberated into the blood stream from the affected area, as hypothesized by several authors, has not been proved. Although adenosine triphosphate, the muscle shock factor, causes a profound fall in blood pressure after injection, it has never induced labor in laboratory animals. While the serum potassium remains within normal limits or is slightly depressed during pregnancy and labor, its rise subsequent to extensive burns is responsible for cardiac standstill and death.

It is of interest that the adrenal cortical hormone secretion found to increase during pregnancy and labor also increases following severe burns, reaching a peak in the latter instance in about 48 hours. The elevation in both conditions may be attributed to stress. It is noteworthy that the onset of uterine contractions in this burn victim coincided with the cortical hormone secretion peak of 48 hours. Another factor to be considered, however, is the adrenal cortical hormone secretion of the placenta. This minute amount along with the loss of a large amount of plasma containing pitocinase is possibly sufficient to effect the release of the posterior pituitary hormone. If so, this may have contributed to the initiation of uterine contractions. Needless to say, further study, investigation, and experimentation will be necessary to clarify the relationship between the endocrine system and labor.

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CLASSIFICATION AND ANALYSIS OF MATERNAL DEATHS IN BRONX COUNTY, NEW YORK, 1946-1957*

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THIS study was made with two objectives in mind: (1) to review all maternal deaths for the past 12 years in the county of the Bronx, New York, with a view to further decreasing maternal mortality, and (2) to classify these deaths according to the most recent acceptable standard classification.

The importance of decreasing maternal mortality is self-evident. The importance of uniformity of classification requires emphasis. Unless a common denominator is used for reporting all deaths, comparable figures have little value. Terms such as "obstetric death" and "maternal mortality" must be clearly defined and used properly. These two expressions should not be interchanged or used as a substitute for each other. The percentage of deaths from various obstetric causes is influenced by the way the mortality rate is computed. Many countries and some states subdivide maternal deaths into obstetric and non-obstetric causes and exclude the latter in computing maternal mortality.[1] Admitting that there is no classification that is infallible and that there is a personal equation in the interpretation of a cause of death, we feel that if a standard basic classification is followed, the difference in reporting will be minimum and thus permit accurate comparison of incidence and mortality.

This study comprises a review of all maternal deaths occurring in the county of the Bronx, from Jan. 1, 1946, to Dec. 31, 1957. For practical purposes almost all births occurred in either private, voluntary, or municipal hospitals of the county. Through the Department of Health, City of New York, every death in the county is brought to the attention of the Chairman of the Maternal Welfare Committee of the Bronx County Medical Society. He in turn assigns an obstetrician to investigate and report on a standard form all the facts pertaining to the case. The Committee, which is made up of obstetricians representing the various hospitals in the county, review these data and evaluate the facts pertaining to etiology, avoidability, and responsibility. Consultation with a pathologist, internist, anesthetist, and other specialists is always available. The complete summaries are then presented for educational purposes designed to assist the profession in improving obstetric care, at bimonthly conferences held at the local Department of Health auditorium. At these conferences, factors of preventability and responsibility are constantly stressed.

*Presented at a meeting of the Bronx Gynecological and Obstetrical Society, New York, March 24, 1958.

In the study all maternal deaths were classified as to their cause and listed under four major headings (Table I). This grouping was based on the classification recommended by the Committee on Maternal and Child Care of the Council on Medical Service, American Medical Association, 1957.[2] The original classification was slightly modified; we grouped all undetermined causes of death as a separate category rather than listing them individually under each of the first three headings.

TABLE I. CLASSIFICATION OF MATERNAL DEATHS

I. Direct Obstetric Causes.—
- A. Hemorrhage
- B. Toxemia
- C. Infection
- D. Vascular accidents (air, amniotic embolism)
- E. Anesthesia
- F. Others

II. Indirect Obstetric Causes.—
- A. Cardiac
- B. Vascular disease (hypertensive vascular disease and vascular embolism)
- C. Reproductive tract disease (uterine and adnexal tumors)
- D. Urinary tract disease
- E. Hepatic disease
- F. Pulmonary disease
- G. Metabolic disease
- H. Others (appendicitis, peritonitis, nonpuerperal)

III. Nonrelated Causes.—
- A. Communicable and infectious diseases
- B. Blood dyscrasias
- C. Malignancy
- D. Suicide
- E. Murder
- F. Accidental
- G. Others

IV. Undetermined.—

A necessary category which should be reduced as much as possible, especially through the use of adequate records and autopsies.

Analysis of Maternal Deaths

During the 12 years between 1946 and 1957 there were 303 maternal deaths in the county of the Bronx. The distribution of these deaths was: white patients 75.6 per cent, Negroes 19.1 per cent, and Puerto Ricans 5.3 per cent. This means that 303 pregnant women lost their lives either during pregnancy, labor, or within 3 months post partum, from causes either related or nonrelated to the pregnancy. This period covered 254,249 live births, an incidence of 11.8 maternal deaths per 10,000 live births. One hundred fifteen of these deaths occurred in municipal hospitals, 91 in voluntary hospitals, and 79 in private institutions. Eighteen additional patients died at home or on the way to the hospital. Autopsies were obtained in 40.5 per cent of these cases. Table II lists the number of maternal deaths and live births that occurred each year from 1946 through 1957, divided into two 6 year study periods for the purpose of comparison.

I. Deaths From Direct Obstetric Causes.—These are defined as deaths resulting from complications of the pregnancy itself, from intervention elected or required by the pregnancy, or resulting from the chain of events initiated by

the complication or the intervention. There were 168 deaths so classified. Deaths from direct obstetric causes were therefore responsible for 55.4 per cent of all deaths, or the equivalent of 6.6 deaths per 10,000 live births.

TABLE II. MATERNAL MORTALITY IN THE BOROUGH OF THE BRONX, 1946-1957

YEAR	NO. MATERNAL DEATHS	NO. LIVE BIRTHS	DEATH RATE PER 10,000 LIVE BIRTHS
Period I.—			
1946	36	22,020	16.3
1947	37	23,923	15.4
1948	36	21,328	16.8
1949	30	20,376	14.7
1950	24	20,104	11.9
1951	24	20,920	11.4
Total	187	128,671	14.5
Period II.—			
1952	23	20,607	11.2
1953	19	20,447	9.3
1954	18	20,960	8.5
1955	17	21,181	8.0
1956	15	20,749	7.2
1957	24	21,634	11.0
Total	116	125,578	9.07
Grand total	303	254,249	11.8

A. Hemorrhage: The most frequent cause of maternal death was hemorrhage, which was responsible for 18.9 per cent of all deaths or constituted 33.9 per cent of the direct obstetric causes (Table III). During the first 6 years (1946-1951) there were 33 deaths due to hemorrhage, or 2.5 deaths per 10,000 live births. In the second period (1952-1957) there were 24 such deaths, or 1.9 deaths per 10,000 live births, a reduction of 24 per cent.

TABLE III. DIRECT OBSTETRIC CAUSES

CAUSE	1946-1951	1952-1957	TOTAL	% OF TOTAL MORTALITY	% OF MORTALITY DUE TO DIRECT OBSTETRIC CAUSE
Hemorrhage	33	24	57	18.9	33.9
Infection	23	8	31	10.2	18.4
Toxemia	17	11	28	9.3	16.6
Anesthesia	17	7	24	7.9	14.3
Vascular accidents	9	11	20	6.6	12.0
"Other causes"	6	2	8	2.6	4.8
Total	105	63	168	55.5	100.

The causes of fatal hemorrhage are listed in Table IV in the order of their frequency. In the first period of this study the picture is somewhat different from what it was in the past 6 years. Uterine atony declined more than 50 per cent; there were no such deaths after 1953. This decline was primarily due to the more liberal use of available blood. The judicious use of intravenous Pitocin by the drip method for postpartum uterine atony also helped to control hemorrhage. Rupture of the uterus which was a very common cause of death disappeared after 1951. This was due to the fact that version and extraction gave way to cesarean section. Blood coagulation defects which were unrecognized as such before 1950 made their appearance in 1954 and 1955. Whereas

there was a reduction in the number of deaths due to abruptio placentae, there was an equal rise in those from placenta previa. We were rather surprised to learn that hemorrhage from ectopic pregnancy became the leading cause of death, displacing uterine atony. Not only was there a slight increase in the number of these deaths during the last 6 years but the greatest number occurred during 1957. It is interesting to note that 80 per cent of these deaths occurred either at home, on the way to the hospital, or shortly after arrival.

TABLE IV. CAUSES OF HEMORRHAGE AND FREQUENCY OF OCCURRENCE

CAUSE	PERIOD I (1946-1951)	PERIOD II (1952-1957)	TOTAL
Ectopic pregnancy	6	8	14
Atony	7	3	10
Ruptured uterus	9	-	9
Abruptio placentae	4	2	6
Placenta previa	2	4	6
Coagulation defects	-	2	2
Retained secundines	2	1	3
Trauma	1	2	3
Inversion of uterus	1	-	1
Laceration of uterus	-	1	1
Postoperative hemorrhage	1	-	1
Adherent placenta	-	1	1
Total	33	24	57

About 86 per cent of these deaths were considered preventable (Table V). Of these, 63 per cent were avoidable on the part of the physician; 33 per cent avoidable by the patient; and 2 per cent each were attributed to the hospital and nurse.

Analysis of professional factors and their frequency of occurrence shows the following (Table VI): 23 cases were due to shortcoming in diagnosis, judgment or management; 4 cases to errors in obstetric technique; 1 case to injudicious delay in timing of a procedure; 2 cases to the failure to obtain timely and qualified consultation; and 1 case to unqualified attendant. Combinations of these factors were common, for instance, shortcoming in diagnosis and judgment was frequently associated with injudicious haste or delay or improper procedure. Failure to obtain consultation occurred with failure to utilize currently accepted methods.

As far as patient preventability is concerned, most of the 16 deaths occurred in the ectopic pregnancy group and were due to failure to seek medical aid before rupture.

B. Infection: Infection is the second leading cause of maternal death in this group because of the large number of criminal abortions. It accounted for 10.2 per cent of all maternal deaths or 18.4 per cent of those with direct causes (Table III).

Deaths from infection have been due to septic abortion, puerperal infection, puerperal septic emboli, and infected ectopic pregnancy.

Criminal abortion resulted in 21 out of 31 deaths. There has been a marked decrease from 1.5 deaths per 10,000 live births to 0.3 deaths per 10,000 live births from this cause during the past 6 years, resulting from the marked effort and campaign against criminal abortions by the office of the District Attorney of the county of the Bronx. The immediate cause of death was chiefly peritonitis and in 4 instances gas bacillus infection.

TABLE V. DISTRIBUTION OF PREVENTABILITY AND RESPONSIBILITY FACTORS IN RELATION TO CAUSE

	PHYSICIAN		PATIENT		NURSE		HOSPITAL		PREVENTABLE TOTAL		NON-PREVENTABLE		UNDETERMINED	TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%		
Direct Causes.—														
Hemorrhage	31	63	16	33	1	2	1	2	49	85.9	7		1	57
Infection	1	4.5	21	95.5					22	70.9	9			31
Toxemia	10	66.7	5	33.3					15	53.5	13			28
Anesthesia	21	100							21	87.5	2		1	24
Vascular accident	2	66.7	1	33.3					3	15	17			20
Others	1	25					3	75	4	50	4			8
Indirect Causes														
Cardiac	9	41	13	59					22	68.7	10			32
Vascular disease	1	50	1	50					2	13.3	13			15
Urinary	4	50	4	50					8	88.8	1			9
Pulmonary	1	100							1	10	9			10
Hepatic											1			1
Others	5	83.3	1	16.7					6	46.1	7			13
Total	86	56.2	62	40.5	1	0.7	4	2.6	153	61.7	93	38.3	2	248

TABLE VI. FACTORS OF RESPONSIBILITY (FREQUENCY OF OCCURRENCE)

FACTORS	DIRECT OBSTETRIC CAUSES						INDIRECT OBSTETRIC CAUSES						
	HEMORRHAGE	INFECTION	TOXEMIA	ANESTHETIC	VASCULAR ACCIDENT	OTHERS	CARDIAC	VASCULAR DISEASE	URINARY TRACT	PULMONARY	OTHERS	TOTAL	
A. Professional (Physician).—													
Inadequate prenatal care			4									4	
Shortcoming in diagnosis, judgment, and management	23		2	6	2	1	7	1	4	1	5	52	
Injudicious haste, delay, or poor timing of a procedure	1		2	2			1					6	
Failure to obtain timely and qualified consultation	2						1					3	
Unqualified attendant	1	1	1	11								14	
Failure to utilize current acceptable methods			1									1	
Errors in technique	4			2								6	
													86
B. Nurse.—													
Failure to observe patient carefully	1											1	
													1
C. Hospital.—													
Failure to have blood bank	1											1	
Error in typing and cross-matching						2						2	
Wrong bottle blood						1						1	
													4
D. Patient.—													
Failure to obtain early care	16		2				7	1	4		1	31	
Failure to follow physician's advice			3		1		6					10	
Criminal abortion		21										21	
													62

All 6 deaths from puerperal infection followed cesarean section and were equally divided between the two study periods. This should alert one to the fact that abdominal delivery is not always an innocuous procedure.

One patient developed puerperal septic pulmonary emboli and died despite antibiotics. She was a multipara who had a normal spontaneous delivery and developed a postpartum and suppurative thrombophlebitis. Autopsy disclosed retained infected placental tissue with septic pulmonary infarcts.

A patient with an infected ectopic pregnancy was admitted late in the course of her infection and died postoperatively of peritonitis.

Twenty-two deaths were considered avoidable (Table V). Only one was attributed to the doctor on the basis that he was unqualified to treat this complication of pregnancy with qualified consultation. This patient was a primipara with a breech presentation who was in labor for 48 hours before a general surgeon was called who decided to do a cesarean section. She died from peritonitis. This happened in 1948.

Twenty-one deaths were attributed to the patient; all were criminal abortions.

C. Toxemia: Twenty-eight patients died as a result of pre-eclampsia, eclampsia, and vascular disease with superimposed toxemia. Toxemia, therefore caused 9.3 per cent of all deaths, or constituted 16.6 per cent of the direct causes (Table III). Actually there were 7 other patients who developed toxemia but their deaths were attributed to infection, pulmonary emboli, and anesthesia, and were thus listed under these headings.

There has been a decrease from 1.1 deaths per 10,000 live births during the first 6 year period to 0.63 deaths in the second period. Eclampsia accounted for 22 deaths, pre-eclampsia, 4, and vascular disease with superimposed toxemia, 2. The immediate causes of death were: pulmonary edema, cardiac failure, cerebral hemorrhage, blood coagulation defect, and cortical necrosis of the kidney.

Fifteen deaths were considered avoidable and assigned as follows (Table V): 10 cases to the physician (66.7 per cent) and 5 to the patient (33.3 per cent). The professional factors involved were (Table VI): inadequate prenatal care, 4; shortcoming in diagnosis, judgment, and management, 2; injudicious haste or delay in timing of a procedure, 2; failure to utilize accepted methods, 1; and unqualified attendant, 1. The hospital shared responsibility in this last death for permitting an unqualified physician to treat a serious complication such as eclampsia without consultation.

The shortcomings on the part of the patients were: failure to follow advice of the doctor, 3 cases, and failure to obtain prenatal care, 2 cases.

D. Anesthesia: Anesthesia is playing an increasingly significant role in deaths associated with pregnancy and labor throughout the country. Between 1946 and 1957 there were 24 deaths due to anesthesia; one death out of 10,594 live births. This represented 7.9 per cent of all deaths or 14.3 per cent of all direct causes (Table III).

We have noted a definite decrease in deaths from this cause since our published study in 1953.[3] During the first 6 years, 17 deaths, or 1.3 deaths per 10,000 live births, occurred, as compared to 7, or 0.5 deaths per 10,000 live births, during the second period—a decrease of 65 per cent.

Spinal anesthesia led the group with 10 deaths; 9 were attributed to shock from the spinal anesthetic and one to meningitis which was probably aggravated by or caused by the spinal injection. Five deaths were due to asphyxia, 4 from aspiration of vomitus proved at autopsy and the fifth from gas when a nitrous oxide tank was substituted for oxygen in error. Four deaths were caused by massive collapse of the lungs, 3 with general anesthesia and one with spinal. This shows that this complication may occur with either type of anesthesia.

Cardiac arrest also occurred on 5 occasions, 3 associated with combined anesthetic agents (2 spinal with Pentothal sodium; 1 spinal with cyclopropane), one followed spinal anesthesia, and the fifth general anesthesia. All these deaths occurred with cesarean section.

Twenty-one deaths (87.5 per cent) were avoidable (Table V); the responsibility for one was undetermined (meningitis). All avoidable deaths were attributed to the physician. The professional factors were (Table VI): shortcoming in judgment, diagnosis, and management, 6; errors in technique, 2; injudicious delay in performance of a procedure, 2; unqualified anesthetist, 11.

E. Vascular accidents: Vascular accidents accounted for 20 deaths and were classified as due to air embolus, 2; amniotic fluid embolus, 1; and puerperal nonseptic emboli, 17. They were responsible for 6.6 per cent of all maternal deaths, or constituted 12 per cent of the direct causes (Table III). There was a slight difference between the two 6 year periods. From 1946 to 1951 there were 9 deaths, or 0.7 per 10,000 live births, as compared with 11 deaths, or 0.9 deaths per 10,000 live births, in the second period.

There was one death from amniotic fluid embolus. Although no autopsy was obtained, the clinical picture appeared rather classical. A 28-year-old gravida vi, para v, was admitted in active labor, after an uneventful prenatal course. Several hours later the cervix was fully dilated and the membranes were ruptured artificially following which she manifested signs of deep shock, cyanosis, and dyspnea, and died on the delivery room table. She received no anesthesia. The uterus was explored after delivery and reported as intact. This was considered a nonpreventable death.

There were 2 sudden deaths from air emboli in early pregnancy, proved by autopsy. They both occurred at home. The history was obtained in one case only. This patient was in the bathroom straining during defecation when she suddenly fell to the floor. Her postmortem examination showed in addition to the air embolus a partial separation of the placenta which most likely served as the entrance for the air into the circulation.

The majority of deaths were associated with nonseptic pulmonary emboli. Since operative trauma, anemia, and toxemia seem to predispose to thromboembolic disease, our cases were reviewed with this in mind. Six patients had cesarean sections. Three had toxemia and 3 had postpartum hemorrhage resulting in anemia severe enough to require transfusion.

The task of deciding avoidability was not easy. Most of the deaths were sudden and nonpreventable. Three, or 15 per cent of the deaths, were voted by the committee as avoidable (Table V). Two, or 66.7 per cent, were assigned to the physician because of shortcoming in diagnosis, judgment, and management. In one instance he failed to recognize the complication; in the other he failed to evaluate it properly.

One woman with a phlebothrombosis of the plantar vessels of the right foot signed out of the hospital against the advice of her obstetrician, despite the fact that all dangers were explained to her. She died from a pulmonary embolus (shown at autopsy) while dressing to go home.

F. "Other obstetric" deaths: Several comments are in order with regard to "other obstetric" deaths. There were 8 such deaths in this category, an incidence of 4.8 per cent of all deaths from direct causes (Table III). Half of these were preventable (Table V).

Blood transfusion therapy was responsible for 4 deaths. In 3 cases, the deaths were assigned to the hospital laboratory because of errors in typing and cross-matching, and sending down the wrong bottle of blood. The physician contributed by not checking the name on the bottle before giving the blood. One death could not be attributed to any obvious error. It was believed that this patient had some subgroup incompatibility which could not be detected.

Of interest is the preventable death from electrolyte imbalance of a patient who had continuous vomiting in early pregnancy and complained of lower abdominal pain. She was operated on for intestinal obstruction which was not found. The responsibility for this death is self-evident.

Two women who had cesarean sections performed by competent obstetricians died from paralytic ileus despite antibiotic therapy; an autopsy was performed on one. Here again we emphasize the risk of cesarean section.

The last death in this group occurred in 1956 from choriocarcinoma of the uterus with metastasis to the brain and lungs proved by autopsy.

II. Deaths From Indirect Obstetric Causes.—These are defined as deaths resulting from disease present before or developing during pregnancy (not a direct effect of pregnancy) which was obviously aggravated by the physiological effects of the pregnancy and caused the death. There were 80 deaths in this group (Table VII). Indirect causes were therefore responsible for 26.3 per cent of all deaths, or 3.1 deaths per 10,000 live births.

TABLE VII. INDIRECT OBSTETRIC CAUSES

CAUSES	1946-1951	1952-1957	TOTAL	% TOTAL MORTALITY	% OF MORTALITY FROM INDIRECT CAUSES
Cardiac	18	14	32	10.6	40.0
Vascular	10	5	15	4.9	18.8
Urinary tract	6	3	9	2.9	11.2
Pulmonary	2	8	10	3.3	12.5
Hepatic	1	—	1	.3	1.3
Others	10	3	13	4.3	16.2
Total	47	33	80	26.3	100

A. Cardiac disease: Heart disease complicating pregnancy is the most frequent cause of death in the indirect obstetric group. There were 32 deaths due to this disease (Table VII). Classification of these deaths showed 27 to be rheumatic in origin, 3 hypertensive, one arteriosclerotic, and another kyphoscoliotic. They made up 40 per cent of the deaths from indirect causes, or 10.6 per cent of all deaths. During the first 6 year period there were 18 deaths, or 1.4 per 10,000 live births, compared with 14 deaths, or 1.1 per 10,000 live births, in the second period, a reduction of 21 per cent.

Twenty-two deaths (68.7 per cent) were considered avoidable (Table V); the physician was responsible in 9 instances and the patient was at fault in 13. The responsible factors pertaining to the physician were (Table VI): shortcoming in diagnosis, judgment, and management, 7; injudicious haste in performing a surgical procedure, 1; failure to obtain timely and qualified consultation, 1. In most instances there was a combination of factors at play. For instance, shortcoming in management was usually associated with inadequate prenatal care and failure to obtain timely and qualified consultation.

The patient was at fault 13 times. In 7 instances she failed to obtain early prenatal care, in 6, she did not adhere to the advice of the physician.

B. Vascular disease: Vascular disease per se accounted for 15 of the 80 deaths from indirect causes (Table VII). It was therefore responsible for 18.8 per cent of those from indirect causes, or 4.9 per cent of all maternal deaths. There was a decline of approximately 50 per cent from this cause during the second period of study. Deaths due to vascular disease were subdivided into four groups, namely cerebrovascular accidents, hypertensive vascular disease (malignant hypertension), vascular thrombosis, and aneurysm. The most common cause was cerebrovascular accident which was responsible for 12 of the 15 deaths. Nine primigravidas and 3 multiparas comprised this group. Two

of the primiparas had hypertension at the twenty-second week of gestation but did not develop toxemia. The ages in this group ranged from 23 to 34 years. In only 3 cases was intracranial hemorrhage associated with labor. Most of the cerebral accidents occurred in the last trimester of pregnancy. One occurred 2 days post partum. It appears that hypertension and the hemodynamic changes of pregnancy rather than the strain of labor were the predisposing causes of the vascular disruption. Autopsies were performed in about half of the cases with the following findings: congenital aneurysm and hypoplastic arteries of the circle of Willis, congenital malformation of the vessels of the left cerebral hemisphere, and intracerebral hemorrhage with extension into the subarachnoid space. The clinical diagnosis was made by spinal tap. Bloody fluid under increased pressure which did not clot on standing was considered a positive criterion for diagnosis. Only one death was deemed avoidable with the responsibility assigned to the physician. This patient was a 33-year-old white multipara, 37 weeks pregnant, who complained of severe one-sided headache. She was treated for sinusitis by drainage. Despite the treatment she continued to complain. No further diagnostic procedures were instituted and she subsequently died undelivered from a right frontal and temporal hemorrhage. Failure to recognize the complication as well as failure to obtain timely and qualified consultation contributed to her death.

Death from malignant hypertension occurred in a 43-year-old multipara who did not seek medical care until the sixth month of gestation. She died in uremia. This death was considered preventable on the part of the patient.

A death due to thrombosis of the internal carotid artery with cerebral encephalomalacia and another one from a rupture of an ovarian artery were deemed unavoidable disasters.

C. Urinary tract disease: There were 9 deaths from urinary tract disease, or 11.2 per cent of those from indirect causes (Table VII). Eight resulted from chronic glomerular nephritis and one from polycystic kidney disease. Most of these deaths were considered preventable; in fact the only death which was deemed unavoidable was that of the patient who had polycystic kidneys and who died on the third day post partum. Autopsy showed cystic kidneys with little cortical tissue present. As to the patients with chronic glomerular nephritis, all died from uremia.

Four deaths were assigned to the patient (Table V) on the basis of failure to seek medical care. Four deaths were attributed to the physician because of shortcoming in diagnosis, judgment, and management. In 2 cases he failed to recognize or evaluate this complication properly and in 2 others rendered inadequate prenatal care. We were pleased to learn that since 1952 there had been only one death from chronic glomerular nephritis.

D. Pulmonary disease: There were 10 deaths from pulmonary disease, which amounted to 12.5 per cent of all those from indirect causes. The increase in mortality during the second period was mainly due to the viral pneumonias occurring in 1957. Several patients died during the Asiatic "flu" epidemic.

There was only one preventable death attributed to the physician because of shortcoming in diagnosis, judgment, and management. This patient, 4 months pregnant, complained of abdominal pains and vaginal staining, and was operated upon for an extrauterine pregnancy. No pathologic condition was found and she developed a fatal postoperative bronchopneumonia.

There were 2 deaths from tuberculosis. One patient died in the puerperium after a premature delivery. This death occurred before the antituberculosis drug era. The last patient died from miliary tuberculosis 5 days post partum. Both these deaths were considered unavoidable.

E. Hepatic disease.—There was one nonpreventable death from hepatic disease in a 40-year-old white multipara who died in the fourth month of gestation from a rupture of esophageal varicosities which were a complication of cirrhosis of the liver.

F. "Other" indirect obstetric causes: This group is varied and interesting. It was responsible for 16.2 per cent of all deaths from indirect causes, or 4.3 per cent of all deaths (Table VII). About one half of the deaths were considered preventable (Table V).

There were 2 deaths from sickle-cell disease; one of these patients died of pneumonia, the other in crisis. Both were believed to be unavoidable deaths.

Intestinal obstruction caused 5 deaths. Four were assigned to responsibility of the physician because of shortcoming in diagnosis, judgment, and management on the basis of failure to recognize the complication and evaluate it properly. This resulted in injudicious delay or timing of the operative procedure. One patient was treated for hyperemesis gravidarum who had an intestinal obstruction.

Four deaths resulted from peritonitis. Two patients had acute appendicitis complicating pregnancy in the middle trimester. One of these deaths occurred as a result of a "blowout of the stump" on the fifth postoperative day. The other was voted as avoidable and attributed to the physician because of shortcoming in diagnosis, judgment, and management. This patient was advised over the telephone to use a cathartic for her nausea, vomiting, and abdominal pain in the midtrimester of pregnancy. She died from peritonitis due to a ruptured appendix. The third patient was a 24-year-old white primigravida admitted in active labor with a rigid abdomen. Shortly after delivery she died in shock with no evidence of excessive blood loss. Autopsy revealed primary peritonitis without any demonstrable cause to account for it. The fourth patient, who was 6 months pregnant, had an intestinal obstruction due to adhesions. A resection of the bowel was necessary and despite adequate antibiotic therapy she died from peritonitis.

The case of a woman who died from status epilepticus was published by the senior author[4] in 1956. This death was attributed to the patient for failure to inform her obstetrician of her illness and thus to receive proper medical care.

The last death in this group was due to hemorrhage from a ruptured spleen. This patient, 8 months pregnant, was admitted in shock with signs of premature separation of the placenta. With blood being administered, a cesarean section was done. Free blood was noted in the peritoneal cavity and further exploration revealed a ruptured spleen. Despite splenectomy and adequate blood replacement she died in irreversible shock. This was considered an unavoidable death.

Here again, the number of deaths in the second 6 year period showed a marked decrease. There were no deaths from peritonitis due to appendicitis. There was only one death from intestinal obstruction and no deaths from sickle-cell disease. Whereas there were 10, or 0.8 deaths per 10,000 live births, in the first 6 year period, there were only 3, or 0.23 deaths per 10,000 live births, in the latter period (Table VII).

III. Deaths From Nonrelated Causes.—Thirty-eight deaths are listed in Table VIII and are self-explanatory.

IV. Deaths From Undetermined Causes.—The causes of 17 deaths could not be determined definitely because of incomplete information. This was due to the following reasons: (1) inadequate hospital records with absence of pertinent information; (2) lack of essential data on patients who died suddenly at home; (3) failure to obtain autopsy in cases where the diagnosis was questionable.

TABLE VIII. NONRELATED CAUSES OF DEATH

CAUSE OF DEATH	NO.
Blood dyscrasia	9
Malignancy	12
Ruptured splenic artery (3 months post partum)	1
Peritonitis	5
Status asthmaticus (1 month post partum)	1
Erythema multiforme bullosum (3 months post partum)	1
Lupus erythematosus (3 months post partum)	1
Aneurysm of aorta (3 months post partum)	1
Cardiac disease (2 months and 3 months post partum)	2
Pheochromocytoma (1 month post partum)	1
Trauma (cerebral hemorrhage due to head injury in fifth month of pregnancy)	1
Tuberculous meningitis	2
Pyelonephritis (spontaneous abortion at 2 months)	1
Total	38

Comment

In 1946 in the Bronx County, New York, there were 16.3 maternal deaths from all causes per 10,000 live births. This number decreased so that in 1956 only 7.2 mothers died per 10,000 live births. In 1957, however, there was an increase to 11 deaths per 10,000 live births.

Analysis of our 1957 cases disclosed that the rise in the mortality rate was due to deaths from viral pneumonia occurring during the Asiatic flu outbreak and from ruptured ectopic pregnancies. These deaths were not due to faulty obstetrics.

We believe the increase in mortality from ruptured ectopic pregnancies is due partly to our modern treatment of pelvic inflammatory disease with antibiotics and partly to the influx of indigent and low-income groups (who fail to seek early medical care) into our community. The antibiotics no doubt have saved many tubes from removal by surgery but such tubes never being completely restored to normal function predispose to ectopic gestation. In our country, the number of births among the non-whites doubled in the past 10 years.[5] All our deaths from ectopic pregnancies in 1957 occurred in this ethnic group. Furthermore, these patients arrived at the hospital either dead or in extremis.

TABLE IX. PREVENTABILITY AND RESPONSIBILITY IN "COMBINED OBSTETRIC CATEGORY"

		NUMBER	%	
Preventable		153	61.7	
Physician	86			56.2
Patient	62			40.5
Nurse	1			.7
Hospital laboratory	4			2.6
Not preventable		93	37.5	
Not determined		2	.8	
Total		248	100	

Considering the first 6 year period, the maternal mortality was 14.5 deaths per 10,000 live births, compared with 9.1 deaths per 10,000 live births in the second 6 year period, a decline of 38 per cent. The mortality rate among the Negro patients during the same period increased 72 per cent, while among the white patients there was a decrease of 25 per cent. Deaths from direct obstetric causes which represent a more accurate index of obstetric mortality decreased from 8.16 deaths per 10,000 live births to 5 deaths per 10,000 live births. This is an improvement of 39 per cent. This indicates good over-all obstetric care. That there is room for ample improvement is evidenced by the fact that 61.7

per cent of the "combined obstetric" deaths were considered preventable (Table IX). By "combined obstetric" deaths we mean the total mortality of the direct and indirect obstetric groups. Of the 61.7 per cent, more than half (56.2 per cent) were physician preventable, while 40.5 per cent were patient preventable. Herein lies a source for decreasing our maternal mortality.

Table VI lists the professional factors which contributed to our maternal deaths. Of 153 preventable deaths "shortcoming in diagnosis, judgment, and management" appeared 52 times; "unqualified obstetric attendant" was noted in 14 instances. Thus we have a total of 66 physician-preventable deaths grouped under two major headings, which if controlled would lower the mortality rate of the combined group from 9.8 deaths per 10,000 live births to 7.1 per 10,000 live births. Furthermore, if by some means we could eliminate the patient factor which occurred 62 times we would then be able to decrease this mortality still further to 4.8 deaths per 10,000 live births. This would be approaching an irreducible minimum which is our obstetric goal.

In a discussion of ways and means to reduce maternal mortality, it became evident that any action taken must be directed primarily at improving the diagnostic ability, judgment, and treatment rendered by the physician. Also, since all instances of preventable deaths assigned to patients occurred either because they failed to seek early care or failed to follow the advice of the physician, attention must be directed at securing patient cooperation. The following recommendations were therefore considered:

Physician.—

A. Education:

1. Postgraduate training especially planned for the general practitioner should be arranged in his own locality, preferably in the hospital where he cares for his patients. This should entail daily rounds and discussions, weekly grand rounds, and attendance at monthly conferences. The lectures and demonstrations given to interns and residents should also include this group. Emphasis should be made on "practical things" which the general practitioner needs. The duration of such courses might vary between six months and one year.
2. Refresher courses from time to time to help him keep up to date in obstetric procedures.
3. Periodic distribution of obstetric literature to all physicians practicing obstetrics. This should include standard obstetric procedures, current concepts in therapy, safeguards and errors, etc. This should also be made as simple as possible.
4. Representation of a member of the Academy of General Practice on the maternal mortality committee. In this way the work of the committee will be familiar to their representative who can spread the gospel to the general physician. Perhaps by this means the attendance at maternal mortality conferences could be improved.
5. Maternal mortality conferences to be instituted in private hospitals which have courtesy staffs but no formal obstetric department. It should be the responsibility of the obstetric consultant who is a member of the Medical Board to review and present all deaths to the physicians practicing obstetrics in that institution. At present when any one physician is found to contribute to more than the usual number of deaths, his courtesy privileges are withdrawn. He then proceeds to go elsewhere. This is not the correct way to reduce maternal mortality in any institution.

B. Obstetric control:

1. Mandatory consultation if the patient is in labor over 24 hours.
2. Qualified consultation for all complications and operative procedures.
3. Formation of a special committee in each hospital to review obstetric errors and to discuss them with the physician involved.
4. Trained anesthetists for "all around the clock" anesthesia. The importance of this is self-explanatory.

Patient.—

The problem of securing patient cooperation resolves itself into a problem of education and service.

A. Education:

1. Continuous education of the public in maternal health and care, with recourse to press, radio and television, and motion pictures. Constant reminders to the public of the importance of early prenatal care and the dangers of not following the physicians' advice is mandatory.

B. Service:

1. A closer relationship between clinic physician and patient. The clinics which see most of the patients of the indigent and low-income groups should be made more attractive by favoring closer relationship between doctor and patient. The latter should not be passed on to a different physician each time she visits the clinic but attempts should be made to have the same doctor follow her throughout her pregnancy. This requires emphasis on clinic organization.
2. Privacy should be encouraged.
3. Formation of maternity classes in the outpatient department to indoctrinate the patient and build up an interest in her pregnancy. An interested patient will not miss her clinic visits.
4. There should be more trained public health nurses in maternity to assist the physician in rendering antepartum, intrapartum, and postpartum care. The nurse should serve as a liaison between physician and patient and help to re-educate the mother.

It is only through a complete program of service as well as education that the patient will cease to be responsible for part of our maternal mortality.

We are fully aware that most of these recommendations are not original; nevertheless we feel that they are not adequately enforced.

Summary

1. A 12 year survey of maternal deaths in the County of the Bronx, New York, divided into two 6 year periods is presented. During this time there were 303 maternal deaths from all causes and 254,249 live births, a maternal mortality rate of 11.8 deaths per 10,000 live births.

2. A marked reduction in maternal deaths from 14.5 per 10,000 live births in the first period to 9.07 per 10,000 live births in the second period is recorded. Deaths from direct obstetric causes declined from 8.16 to 5.0 per 10,000 during the same period.

3. The lowest death rate occurred in 1956 when 7.2 mothers per 10,000 live births died from all causes.

4. Hemorrhage stands out as the most frequent direct cause of maternal death, followed by infection, toxemia, and anesthesia. Heart disease and vascular disease are the two leaders among the indirect obstetric causes.

5. Preventability of deaths in the "combined obstetric" category is discussed. Sixty-one and seven-tenths per cent of the deaths in this category were considered preventable; 56.2 per cent were avoidable on the part of the physician while 40.5 per cent were the responsibility of the patient.

6. The factors of responsibility are outlined and the most frequent ones commented upon.

7. Recommendations for reducing maternal mortality are submitted.

We wish to express our gratitude to Dr. Milton J. Goodfriend for his valuable suggestions in the preparation of the manuscript and to Miss Frieda Greenstein, senior statistician, New York City Department of Health, Bureau of Records and Statistics, for the valuable statistical information included in this study. We are also indebted to the members of our Committee who investigated these cases.

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2. A Guide for Maternal Deaths Studies: Committee on Maternal and Child Care of the Council on Medical Service, American Medical Association, 1957.
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4. Klein, M. D., Goodfriend, M. J., and Shey, I. A.: Am. J. Obst. & Gynec. 72: 188, 1956.
5. Bureau of Records and Statistics, Department of Health, New York City: Personal communication.

1882 Grand Concourse
1749 Grand Concourse

DEPARTMENT OF CURRENT OPINION

Clinical Problems

ADRENAL CORTICAL TUMOR

Case Presentation

DURING the preceding 4 months a 3½-year-old child had had three episodes, lasting 4 or 5 days, of bloody mucoid or mucopurulent vaginal discharge. She was well nourished and happy. Cribside examination revealed the following positive findings: She had some facial acne. There was a light growth of hair on the sides of her face and in the axilla. The breasts were slightly, but definitely, enlarged with some darkening of the areolas. Pubic hair growth, her first symptom, had begun one year before examination and was now quite heavy. The clitoris was enlarged, bulbous, and seemed somewhat edematous. The external genitals were plump, moist, succulent, and structurally normal.

Problem: What suggestion could you make that might be diagnostically helpful?

Consultation

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PROFESSOR OF OBSTETRICS AND GYNECOLOGY AND HEAD OF THE DEPARTMENT, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

This child demonstrates precocious sexual development of a mixed type. The vaginal bleeding and breast development suggest hyperestrogenism. The acne, facial hair, and enlarged clitoris suggest precocious development from excess androgen stimulation. A mixed type of precocious sexual development often is accompanied by Cushing's syndrome from hyperadrenocorticism. The primary pathologic condition causing the physical changes described in a girl of this age is most likely a functioning adrenocortical carcinoma

which secretes both estrogen and androgen. The suprarenal areas should be carefully palpated for evidence of tumor. A rectoabdominal bimanual examination should be made since an adrenal-rest tumor of the ovary may be the primary seat of disease. An intravenous pyelogram should be of help in localizing a suprarenal tumor if such a tumor cannot be palpated.

It would be expected that the 17-ketosteroids and the 11-oxysteroids would be elevated. A study of the exfoliated vaginal epithelium would probably show a cornified type of vaginal cell on the stained slide.

The blood pressure would be expected to be elevated. Other physical findings that may be present are relative obesity, skin striae, and pseudodiabetes.

It would be very unusual for a mixed type of precocious puberty to develop from cerebral causes. Adrenocortical hyperplasia (primary) does not cause precocious sexual development in a child this young.

My diagnosis is functioning adrenal cortical tumor producing an early Cushing's syndrome.

If the 17-ketosteroids and 11-oxysteroids were reported as normal, I might have to consider the diagnosis of precocious isosexual development, secondary to a functioning ovarian tumor or constitutional causes. My opinion is, however, that, when all the information is in, the diagnosis of functional adrenal cortical tumor will be substantiated. Surgical exploration of the suprarenal area with excision of the tumor is indicated. It is extremely important that this child have proper preoperative, operative, and postoperative support of her adrenal physiology with corticosteroid therapy. The reason for this is that the functioning adrenal cortical tumor may be accompanied by adrenal atrophy on the opposite side. Removing a functioning adrenal cortical tumor without proper support of the patient with cortisone is a serious error and may lead to the death of the patient.

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The case outlined presents a problem in the diagnosis of precocious sexual development and menstruation. Even with such obvious signs, however, the gynecologist should not presume that the bloody mucoid or mucopurulent vaginal discharge could not be due to more than one factor, namely, the concomitant presence of a foreign body in the vagina in addition to precocious sexual development. For that reason, the following steps should be taken: The child should be admitted to a hospital and after adequate acclimation to the surroundings of the Pediatric Surgical or Pediatric Gynecologic Service, an examination under anesthesia, colposcopy, a vaginal smear, and an endometrial biopsy should be performed. During the examination under anesthesia, the presence of enlarged and possibly cystic ovaries or the presence, on the contrary, of small, firm ovaries should be noted. In rare instances, a granulosa-cell tumor with secondary sex changes, but an anovulatory type of menstruation, is found. These tumors, however, because of the rigid shelf presented by the uterus, the broad ligaments, and the as yet undeveloped skeletal framework of the pelvis, almost invariably can be felt abdominally and, even though not large, present as abdominal tumors rather than as a pelvic mass. During the course of this examination, the clitoris, crura of the clitoris, and the remaining structures of the vulva are further

studied, as well as the breast development. The extent of hair growth on the face, in the axilla, and on the mons veneris is carefully described. An enlarged, bulbous, and edematous clitoris suggests strong estrogen stimulation.

After these preliminary studies and provided the facilities are available, the urinary excretion of 17-ketosteroids, urinary gonadotrophin, and urinary estrogen determinations can be done; but, because of the technical limitations of tests of this type, they cannot be considered incontrovertible evidence of one type of sexual precocity or another. To continue the study of the patient, an x-ray of the epiphyses of the long bones should be taken to see if the somatic development parallels the precocious sexual development with premature closure of the epiphyses of the long bones.

An x-ray of the sella turcica might be informative if a tumor in that region or an intracranial lesion of the hypothalamus is suspected. If an intracranial lesion were probable, together with true sexual precocity, i.e., ovulation, mature follicles, and a luteal phase in the menstrual cycle, further studies would have to be conducted by a neurologist or neurosurgeon to determine the exact site of the lesion and whether or not it was an expanding intracranial lesion causing the syndrome.

Of all patients with premature sexual development studied, less than 15 per cent will be found to have a specific abnormality of the ductless glands or the central nervous system responsible for the syndrome. It is still the gynecologist's responsibility to carry out the tests that are available to him in his clinic. Unfortunately, in the absence of a specific lesion that can be removed, there is little that can be offered these children in regard to hormone therapy to arrest the process and it becomes, for the most part, a problem of their psychosexual management so that they are not disturbed emotionally. The child, depending on her comprehension of the problem, should be reassured and it should be repeatedly emphasized that she is not any different from other children, but simply, perhaps, got a head start on her sisters. Her parents should be reassured that, despite the premature sexual development, the sexual urge and libido do not follow such premature sexual development. They need entertain no worries regarding the child's becoming abnormal sexually, and emotionally involved with older male adolescents because of this premature development of the sexual organs and secondary sexual characteristics.

Pertinent references are given for those interested in further study.

References

Stemfel, R., and Migeon, C. J.: Clin. Obst. & Gynec. 1: 271, 1958.
Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, ed. 2, Springfield, Ill., 1957, Charles C Thomas, Publisher.

Editor's Comment

The vaginal bleeding and succulent genital tissues suggested a response to estrogen. No estrogen therapy had been administered. Hair growth, acne, and enlargement of the clitoris suggested androgenic stimulation. The combination suggested that the child had a gynandroblastoma of the ovary, a pituitary disorder, or adrenocortical hyperfunction. A gynandroblastoma of the ovary has not been reported in a premenarchal child. Congenital adrenocortical hyperplasia was excluded because the genitals were morphologically normal. Roentgenologic studies of the skull and sella turcica were normal. The bone age was not advanced. A vaginal cytosmear disclosed cornification of the vaginal epithelium. The uterus was found to be slightly

enlarged and the ovaries of normal size on rectoabdominal palpation. Palpatory findings were verified by roentgenography after pneumoperitoneum. Examination of the upper abdomen demonstrated a small mass in the deep right lateral upper quadrant. Presacral insufflation followed by roentgenography revealed a mass above the right kidney and occupying the position of the right adrenal gland. A urogram showed the right kidney displaced downward. The 17-ketosteroid excretion was 12.0 mg. in 24 hours. A diagnosis of an adrenocortical tumor was made and confirmed by surgical exploration. The histopathologic diagnosis was adenocarcinoma of the adrenal cortex. Following its excision, abnormal hair growth, acne, breast enlargement, genital bleeding, and other signs of hormone stimulation gradually disappeared.

MISSED ABORTION

Case Presentation

MRS. A. M. is 37 years old, white, para ii, gravida iii, of a good socioeconomic background. Her last menstrual period was on July 18, 1957.

Her previous pregnancies and deliveries had been normal in every respect. The last pregnancy was 12 years previously.

Prenatal visits during the present pregnancy began shortly after the first missed period and she seemed to be progressing normally. Shortly after quickening, which had been noted Dec. 12, 1957, disappearance of all fetal movement followed by breast secretion announced the intrauterine demise of the fetus. She followed the advice of her obstetrician to let nature take its course. Muddy and slightly malodorous vaginal discharge was her only symptom. There were no signs of labor until March 10, 1958, when she complained of one severe lower abdominal pain which eased after 10 minutes.

Her physician advised admission to the hospital. The hemoglobin was 13.5 Gm. per cent; the leukocyte count was 11,500 with 83 per cent polymorphonuclear cells; the fibrinogen level was normal; the temperature was 99° F., pulse 80, and respirations 20; a catheterized urine specimen contained a few white blood cells in each high-power field. A pregnancy test was negative. Examination disclosed a symmetrically enlarged uterus with the fundus 6 cm. below the umbilicus. The adnexa were normal. The cervix was unusually long and firm with no dilatation. There was no loss of the cervicofundal angle. The enlarged, slightly boggy uterus failed to contract when massaged between the examining fingers. Such efforts elicited a moderate amount of pain.

Problem: What is your recommended management of this case?

Consultation

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The statement that "examination revealed a symmetrically enlarged uterus with the fundus 6 cm. below the umbilicus" permits the assumption that we have to deal here with a pregnancy located in the true uterine cavity. Since on Dec. 12, 1957, or at the twentieth week of pregnancy approximately, the fundus should have been at the level of the umbilicus, it is evident that it had undergone pronounced diminution in size by March 10, 1958, when it was 6 cm. below the umbilicus. This, and other facts mentioned in the history, indicate that we are dealing with a missed abortion in which the dead fetus has been carried for 3 months without expulsion.

The best course to pursue in this case is to await spontaneous expulsion of the products of conception. Although cases are on record in which dead

fetuses in utero have been carried for years, these are museum pieces of the greatest rarity, especially in pregnancies of this duration. If we except these rare curiosities, 5 months is about the limit for a fetus of this size to be retained in utero. This means that in the present case we have only 2 months to go; and since the patient has been resigned to a waiting program over the past 3 months, she would probably be willing to wait a little longer.

During the waiting period, however, estrogens might well be tried. Estrogens are moderately efficacious in promoting expulsion of the fetus in cases of missed abortion and, even if not effectual, they serve to beguile the time. Kurzrok[1] has reported excellent results with ethinyl estradiol marketed under the trade name of Estinyl,* in doses of 0.3 Gm. for 6 days. Others have had fairly good results with diethylstilbestrol. Since Pitocin has no oxytocic effects in the first half of pregnancy, even with a living fetus and normal hormonal-vascular relationships, it seems unlikely that it would be helpful in missed abortion, and it is not recommended.

If the products of conception have not been expelled by the end of 5 months, despite estrogen therapy as mentioned, you are dealing with a very unusual and "stubborn" case of missed abortion. In that event, I would recommend abdominal hysterotomy for removal of the products of conception. This may sound radical but dilatation of these closed, rigid cervices as are usually present in missed abortion, has led to so many lacerations, perforations, and hemorrhages that I do not feel that vaginal interference in missed abortion has any place in modern obstetrics.

Although the fibrinogen level has remained normal thus far, plasma fibrinogen estimations should be made every week and if the level falls to less than 150 mg. per 100 c.c., immediate abdominal hysterotomy should be performed.

The findings in this case correspond fairly well with missed abortion. The sudden pain may have been due to a brief, spasmodic, but ineffectual effort of the uterus to expel its contents, while the uterine tenderness may have been attributable to resultant placental separation. Failure of the uterus to contract on stimulation is common in missed abortion.

In cases of this kind it is extremely important to rule out advanced tubal pregnancy, abdominal pregnancy, and pregnancy in a rudimentary horn of the uterus. Unless the examiner in this case has been mistaken in his reference to the "uterus," the statements in the case history eliminate the first two conditions. Careful bimanual examination, if necessary under anesthesia, should permit palpation of the normal nonpregnant uterine body in cases of gestation in a rudimentary horn. Even if you miss this diagnosis, however, no harm is done by the management recommended since at laparotomy the condition will at once become apparent and can be handled at that time as circumstances dictate.

Reference

1. Kurzrok, L: Am. J. Obst. & Gynec. 56: 796, 1948.

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*Schering Corporation, Bloomfield, N. J.

M. Edward Davis, M.D., Chicago, Ill.
Joseph B. DeLee Professor of Obstetrics and Gynecology, and Chairman of the Department, University of Chicago School of Medicine, Chief of Service to Chicago Lying-in Hospital

The intrauterine death of a fetus at about 18 weeks' gestation is an uncommon occurrence. The safest treatment for missed abortions at this late date is to await the spontaneous onset of labor. This is not always easy to do, for the patient and her family may urge the physician to terminate the pregnancy artificially to relieve the anxieties and emotional pressures of carrying a dead baby. There is no evidence that the patient can absorb toxic products from the degenerating conceptus. The hazard of intrauterine infection is small if there are no intravaginal or intrauterine manipulations. Fisher[1] analyzed 30 cases of missed abortion with the retention of uterine contents for 2 to 6 months. The most favorable course followed the spontaneous onset of labor.

The patient most often will develop increasing uterine irritability manifested by uterine cramps. Labor will finally set in and usually spontaneous evacuation will follow in a short time. Prophylactic antibiotic therapy may be started with the onset of labor and continued for several days after the evacuation of the uterus.

Should uterine activity be initiated by the intravenous drip of an oxytocic drug? This may be effective when the patient exhibits irregular uterine contractions and some cervical effacement has taken place; however, labor is extremely difficult to initiate at this period of gestation. Repeated attempts at the induction of labor may disturb normal intrauterine relationships favoring the ascent of organisms from the lower genital tract and the development of an intrauterine infection.

Operative intervention by cervical dilatation and the artificial evacuation of the uterus at this period of pregnancy are hazardous and may result in serious trauma. Evacuation of the uterus by hysterotomy is a major procedure and is rarely indicated.

Reference

1. Fisher, G. G.: Obst. & Gynec. 1: 529, 1953.

Editor's Comment

On the day of admission the local consultant advised repeated attempts to prepare the cervix by intravenous use of Pitocin. It was also suggested that fibrinogen levels be determined daily. The patient's doctor ordered 2½ ounces of castor oil prior to the use of the intravenous Pitocin. The patient went into violent labor and was delivered of the macerated abortus in about 2 hours without having received any intravenous medication. Her subsequent course has been uneventful.

Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

The Clinical Application of Hormone Assay. By John A. Loraine. 368 pages, 66 figures, and 20 tables. Baltimore, 1958, Williams & Wilkins Company. $7.00.

Current methods of hormone assay and a discussion of their clinical applications are presented. Most of the present assay methods are given and the most reliable methods are emphasized. The author strongly urges that chemical assays replace biological methods where the former have proved accurate.

The material deals mostly with the pituitary, placental, adrenal, and gonadal hormones. The parathyroid and gastrointestinal hormones are not included. The thyroid hormones are not considered since the author believes assay methods for the thyroid hormones are not at present suitable for clinical application.

More space is given to the techniques of assay than to their clinical application. As a result, the book is of more value to the laboratory endocrinologist than to the clinician and probably, therefore, will find a limited acceptance.

Modern Trends in Endocrinology. By Harold Gardiner-Hill. 311 pages with 15 figures, 8 tables and 1 plate. New York, 1958, Paul B. Hoeber, Inc. $13.50.

An attempt is made to correlate the research work and clinical experience in the field of endocrinology for the past few years. There are twenty-one separate chapters dealing with different aspects of endocrinology and written by authorities in their particular fields. The advances in each field are brought out but the author's personal views are often included.

Since much of the recent research in endocrinology involves the adrenal hormones, considerable space is devoted to this phase of the subject. Actually seven chapters are devoted directly to this aspect of endocrinology.

The chapter on the hormonal factors in breast development and milk secretion is most interesting and informative.

Another topic which is discussed quite adequately and which usually receives little if any attention is the relationship between carcinoid tumors and serotonin.

The format of the book is good and there is a minimum of confusing statistics. This book should find widespread acceptance among workers in the field of endocrinology.

Essentials of Gynecology. By E. Stewart Taylor. 502 pages, 343 figures, 4 plates, and 7 tables. Philadelphia, 1958, Lea & Febiger. $12.00.

One gets the impression throughout this book of a fresh and independent approach. The author has written a textbook to meet the needs of undergraduate students and young

practitioners of gynecology. He has succeeded admirably in presenting the essentials of the subject in a concise, straightforward manner.

The chapter on Preventive Medicine in gynecology is a welcome innovation. Thorough examination of the breast is described, as well as self-eaxmination by the patient. A chapter on "Pediatric Gynecology" presents a neglected subject.

Malignancies of the generative tract are emphasized, including a well-balanced description of both operative and irradiation treatment.

The usual operative techniques are fully discussed and well illustrated. Short historical sketches introducing some subjects add interest.

Oestrioluitscheiding in de Urine en de Anatomische Toestand van de Placenta Special bij Toxaemie. By G. J. W. H. Lenters. 160 pages, 18 tables, 3 graphs, and 3 figures. Groningen, 1958, J. B. Wolters.

In the mildest cases of toxemia of pregnancy (blood pressure below 130/80), normal urinary excretion of estriol usually was found (in 61 per cent). When the blood pressure ranged from 130/80 to 160/100, 42 per cent were found to have normal estriol excretion. Moreover, the estriol excretion increased somewhat as pregnancy progressed in these cases. In the more severe cases of toxemia, estriol excretion was subnormal and did not increase as pregnancy went on.

Estriol excretion was correlated with the histologic appearance of the placenta. In general, the poorer the condition of the placental epithelium, the less estriol was excreted. Placental weights and fetal weights also were correlated with estriol excretion.

Endocrine Pathology of the Ovary. By John McLean Morris and Robert E. Scully. 151 pages, 75 illustrations, and 7 tables. St. Louis, 1958, The C. V. Mosby Company. $8.50.

Tumors of the ovary which have endocrinological aspects have provoked much discussion as to classification and origin. Consequently any work which tends to correlate and clarify present knowledge of this problem deserves attention. Such a book is the one under discussion.

The chapter on the various conditions associated with polycystic ovaries is quite complete. It gives a clear picture of the various pathological variants. The suggestion that some of these conditions are due to androgen-producing cells in the medulla is corroborated by some recent experimental work where the medulla has been removed in certain cases of the Stein-Leventhal syndrome.

Although many of the tumors described are seen only rarely in the average clinic, the descriptions are so complete and clear that their identification should be simple.

The format of the book is most pleasing so that reading is easy. The illustrations are unusually clear so that the features described are discernible and make for proper understanding.

A Modern Practice of Obstetrics. By D. M. Stern and C. W. F. Burnett. Second edition. 258 pages, 141 figures. Baltimore, 1958, Williams & Wilkins Company. $9.00.

The second edition of a book first published in 1952 is now revised and brought up to date. Among the new subjects discussed are hypotensive drugs, pain during pregnancy, hypofibrinogenemia, and amniotic fluid embolism. The authors' aim has been to write upon the subject from a new aspect and in this respect they have not been very successful.

In persistent occiput posterior position they advise that delivery should be effected with the face to the pubes though they admit that a greater circumference passes the outlet with this mechanism. They then advise an attempt at manual rotation and state also that the head is turned easily by the use of Kielland forceps. In breech delivery the Wigand maneuver is not mentioned and they do not seem quite clear as to the circumstances under which the Prague maneuver is indicated. They describe such relics of the past as the cranioclast, cephalotribe, and blunt hook.

BOOKS RECEIVED FOR REVIEW

Callander's Surgical Anatomy. By Barry J. Anson and Walter G. Maddock. Fourth edition. 1157 pages with 1047 illustrations. Philadelphia, 1958, W. B. Saunders Company. $21.00.

Clinical Endocrinology. By Karl E. Paschkis, Abraham E. Rakoff, and Abraham Cantarow. Second edition. 941 pages with 274 illustrations. New York, 1958, Hoeber-Harper. $18.00.

Immunity in Pregnancy. By Clarence Malmnas, translated from the Swedish by Viktor Braxton. 106 pages, 54 tables, and 16 figures. Stockholm, 1958, Almquist and Wiksells.

La Terapia del cancro dell'utero. Edited by Prof. A. Brunschwig. 435 pages, 9 illustrations, 66 figures, and 77 tables. Torino, 1957, Edizioni Minerva Medica.

SELECTED ABSTRACTS

The American Journal of Pathology

Vol. 34, May–June, 1958.

Daniel, Peter M., and Prichard, Marjorie M. L.: The Effects of Pituitary Stalk Section in the Goat, p. 433.

Thirteen male goats were operated on for section of the pituitary stalk with interposition between the sectioned edges of a wax plate. This procedure was done successfully in 9 cases and in 3 cases section was not achieved. There was merely simple displacement of the stalk by the pressure of the wax disc. The animals were sacrificed at varying intervals, from 25 hours to 29 days with immediate complete necropsy. Five normal goats were used for a study of the pituitary blood supply by the injection under pressure of a latex compound into the external carotid artery.

The results showed that the pituitary glands of the animals sacrificed 25, 52, and 72 hours postoperatively were noticeably shrunken with *almost* complete infarction of the anterior lobe, save for a rim of viable hypophyseal cells. Notable is the fact that there was an absolute increase in the bulk of viable tissue in the pars distalis in the goats sacrificed after one to 3 days and this increased with the longer survival times. Numerous mitotic figures were discovered around the areas of infarction in specimens sacrificed at one to 3 days.

The significant change in the pars intermedia was hypertrophy of that portion as the survival time increased.

Neural elements in all portions distal to the section degenerated. In the animals in which the stalk was merely pushed aside and not severed, there was a localized area of second-degree infarction to pressure due to encroachment on only a portion of the blood supply. These pituitaries with localized areas of infarction showed relatively the same changes, such as scarring, retraction, increased mitosis, and hypertrophy, as did those with true section of the stalk, only on a more localized scale.

The study of the blood supply indicated that the left anterior pituitary and its blood supply were similar to that of man in that the sole blood supply to the anterior lobe was via the hypophyseal portal system in the pituitary stalk.

Evidence seems to show that the pathologic picture seen in the severance of the pituitary stalk of goats is comparable to the lesion seen by Russell in a case of accidental pituitary stalk section in man and, more important, the changes are comparable to the lesion seen in acute postpartum anterior pituitary necrosis. This last fact leads the authors to support strongly the view that that syndrome results from impairment of the blood flow through the pituitary stalk. This impairment could arise in either the anterior hypophyseal arteries, the pituitary stalk's hypophyseal portal system, or the capillary bed in the pituitary stalk.

Another intriguing problem was that of regeneration. Did the mitotic figures, located mainly around the site of infarction, represent regeneration? If so, were these cells along with the remaining viable cells capable of exerting endocrine function in spite of loss of major sources of blood? These questions are yet to be studied. Their answers will determine whether or not pituitary stalk section will be of value in the control of a carcinomatous process.

LAWRENCE SONDERS

Acta geneticae medicae et gemellologiae

Vol. 7, April, 1958.

Gingras, G., Lemieux, R., Susset, V., Chevrier, J. M. and Suirion C.: Twins and Cerebral Palsy, a Combined Study, p. 249.

This communication reports the experience of the Rehabilitation Institute of Montreal, where they have been following 250 cases of cerebral palsy. They found three pairs of monozygotic twins, one in each pair of which had the disease. All children were subjected to physiatric, psychiatric, and psychological studies, as well as tests involving activities of daily living. The study also included encephalograms, still and motion pictures. The psychological and psychiatric status of the parents was also evaluated. The major findings were:

1. The same somatotype was found constant in each set of twins in spite of apparent physical discrepancies.
2. Though seizures occurred in only one case, the electroencephalograms demonstrated epileptic potentials in each of the three cerebral palsied children.
3. There is a constant discrepancy in I.Q. in favor of the normal twin.
4. The normal twins have a tendency to identify with the parent of the opposite sex.
5. The psychiatric conclusions were very closely related to the psychological make-up of the parents.

This painstaking, complete, and clearly presented study is recommended to anyone interested in the problem of cerebral palsy.

SCHUYLER G. KOHL

Anais brasileiros de ginecologia

Vol. 45, May, 1958.

Fernandes, M., Junior, J. C., and Fernandes, R.: The Intra-amniotic Injection of Prostigmin Methylsulfate for the Induction of Labor, p. 323.

A small series of 53 cases of labor induced for a variety of reasons by the simple method of the transabdominal, intra-amniotic injection of Prostigmin methylsulfate in doses of 1 to 2 mg. is reported, with a success rate of 88.7 per cent. This method has superseded the injection of hypertonic saline by the same route which had resulted in a high fetal loss. There were no maternal deaths and no deaths of fetuses alive at the time of induction. It should be pointed out that 24 of the 53 fetuses were dead at the time of induction. From the list of indications, 24 inductions were done because of a dead fetus. It is difficult to determine why this fact constituted an indication for induction. In view of the modern methods of induction of labor, viz., artificial rupture of the membranes and intravenous oxytocics, this particular method is most fascinating because of the unusual approach to the subject.

FRANCIS B. O'BRIEN

Bulletin de la Société royale belge de gynécologie et d'obstétrique

Vol. 27, December, 1957.

Limage, J.: The Need for Caution in the Diagnosis of the Stein-Leventhal Syndrome, p. 657.

The author maintains a reserved attitude toward the Stein-Leventhal syndrome. Aside from the considerable variability of the symptoms presented by the patients reviewed, he finds variation in the histology of the ovarian wedges resected: the tunica albuginea varies in thickness from one area to another; the degree of hyperthecosis varies; no stromal luteinization was noted. The most constant characteristic was the presence of peripheral cysts. The author avows his dissatisfaction with present laboratory techniques used in diagnosis: cases of Stein-Leventhal syndrome with elevated 17-ketosteroids have been reported; the cortisone test is not sufficiently sure; his own method of fractionating the 17-ketosteroids, which shows elevated fractions IV and V, has been criticized by Jailer and Van de Wiele. Limage believes that the similar pre- and postoperative levels of the 17-ketosteroids and their fractions speak against a gonadal origin for the presumed abnormal androgenic substance. No satisfactory explanation for the elevated pregnanediol complex, or for the thickened tunica albuginea, is at hand. In conclusion, the author states that, although the histopathology of the ovary is well known, the function of the adrenals and pituitary is poorly understood. The only certain fact is the surgical result, which is good but blind; it is therefore dangerous, since it may lead to abuse of wedge resection with consequent failures.

DAVID S. WERMAN

Plate, W. P.: The Surgical Pathology of the Stein-Leventhal Syndrome, p. 671.

The author describes the typical bulky gray-white ovary, with its smooth and glistening surface. The tunica albuginea is frequently thickened; beneath it are a large number of follicle cysts of varying size, whose granulosa layer is often thinned out. Fibrosis of the stroma is occasionally noted, while luteinization of the theca externa is rare. The author poses the question: Does the Stein-Leventhal syndrome represent early virilism, with its origin in the ovary itself? Androgenic substance, he believes, may be produced normally in the ovary, and be necessary for ovulation. If for any reason this fails to occur, LH levels rise, causing hyperthecosis of the theca interna as well as an elevation of androgen.

Of 98 patients who underwent wedge resection, 88 showed hyperthecosis. Among 82 of the original group, who had been anovulatory, 68 showed hyperthecosis. In lieu of a control series, the ovaries removed from patients for various unrelated reasons were examined and only 9 specimens showed hyperthecosis out of 49 examined. Furthermore, of the above-mentioned 68 patients with hyperthecosis, 57 per cent ovulated following wedge resection, while only 29 per cent of those without hyperthecosis ovulated following operation. The author believes this shows a statistically significant correlation between anovulation and hyperthecosis.

DAVID S. WERMAN

Netter, Albert, and Lambert, Alice: Toward a Definition of the Stein-Leventhal Syndrome, p. 680.

The authors maintain that the Stein-Leventhal ovary and syndrome represent a special form of the classical "sclere-cystic" ovary, which they refer to as "polycystic ovarian dystrophy." In this closely reasoned paper they criticize two current tendencies: one in which all micropolycystic ovarian disease is labeled Stein-Leventhal syndrome; the other, in which all cases comprising infrequent menstruation associated with hirsutism are classified under the entity. Criticisms are also leveled at Shippel's single criterion of thecal hyperplasia, and Jackson and Dockerty's attempt to demonstrate that the Stein-Leventhal syndrome predisposes to corpus carcinoma (which they, the authors, reject on grounds of inadequate statistical methodology).

Netter and Lambert's own definition of the syndrome is summarized in the following points: (1) permanently irregular periods, with at least one cycle a year lasting longer than

80 days; (2) progressively infrequent ovulation: zero to three times a year at most; (3) hard, smooth ovaries of constant volume; (4) lack of response to cortisone and its derivatives; (5) generally progressive character of the symptoms; (6) onset of the syndrome before 20 years of age; (7) white, smooth, pearllike ovaries noted at laparotomy or on celioscopy.

Regardless of the initial diagnosis, the authors recommend an attempt at medical management prior to operation, i.e., weight reduction, cortisone, progesterone, etc. These will be without effect in the Stein-Leventhal syndrome. A good response to wedge resection is almost pathognomonic.

DAVID S. WERMAN

The Lancet

Vol. 1, January 11, 1958.

Gibberd, G. F.: The Choice Between Death From Postmaturity and Death From Induction of Labour, p. 64.

The presumption is made that fetal deaths due to postmaturity are due to placental insufficiency and the resultant anoxia. The fatal effect of anoxia could be manifest by: (1) prenatal death (a macerated fetus), (2) intranatal death, and (3) postnatal death. In all of these no cause for the death other than anoxia can be discovered in either the mother or in the infant. At the Queen Charlotte's Hospital in London in 1951-1953, 7,965 infants were delivered after the thiry-sixth week of gestation. Of these, 65 infants died of no known cause other than anoxia, and the mortality per 100 births in pregnancies that completed 41 weeks or more was 1.1 as contrasted to 0.85 in pregnancies that completed 37 to 40 weeks (0.5 in pregnancies lasting 39 or 40 weeks). Assuming that there is a method of induction of labor which is infallible and entirely safe, the calculation is made that induction of labor before the forty-first week (2,600 possible occasions in the present series) could not have saved more than 14 infant lives, or if the induction is postponed to the forty-fourth week (115 occasions) not more than 2 infant lives. Such an ideal method for induction does not exist, however. In a series of 68 inductions for postmaturity, 4 stillbirths occurred. Appreciation of the dangers of postmaturity must be balanced against the dangers and fallibility of current methods of induction.

DAVID M. KYDD

Ashley, D. J. B., and Jones, C. H.: Sex Reversal: Ovarian Tissue Associated with Male Nuclear Sex, p. 74.

A child was examined first at the age of 10 days because of doubts concerning its sex. The child appeared to be a female with an enlarged clitoris on which was a hypospadic urethral orifice. In front of the anus was a vagina with a second urethral opening. Subsequently it was found that a single urethra left the bladder which shortly divided into two. No other physical abnormalities were detected. When tested on 3 occasions, the child excreted a normal quantity of 17-ketosteroids (0.64, 0.22, and 0.25 mg. per day). Four smears of the buccal mucosa and a skin biopsy all showed male sex chromatin. Three separate blood films were examined and in each more than 6 "drumsticks" were seen among every 500 cells. At the age of 17 months a laparotomy was performed. A uterus and Fallopian tubes that appeared to be normal were seen. The ovaries were slightly enlarged and cystic. No sign of testicular tissue was found. Histological examination of a small portion of the right ovary showed a follicular cyst and that many oogonia and a few formed Graafian follicles were present.

The discrepancy between the results obtained from examining cells obtained from the buccal membranes and those in the blood smear has been reported previously by others. The histological appearance of the ovary presents a more serious discrepancy in that all the usual structures of the ovary, including germinal centers, are present in this patient whose nuclear sex, as judged by epithelial cells, is male. Certain features of female pseudohermaphroditism, Turner's syndrome, gonadal agenesis, Klinefelter's syndrome, and true hermaphroditism are

reviewed and the conclusion is reached that in the present case the embryogenesis can best be explained as due to the ascendancy of an abnormal female evocator acting on the indifferent gonad in the earliest days of intrauterine life.

DAVID M. KYDD

Vol. 1, April 5, 1958.

Muller, A. F., Manning, E., and Riondel, A.: Influence of Position and Activity on the Secretion of Aldosterone, p. 711.

The diurnal and nocturnal excretion of aldosterone, 17-hydroxycorticosteroids, potassium, and sodium was determined in 3 healthy subjects and one patient with hypophyseal dwarfism. One normal woman who ate and slept regularly always excreted larger amounts of aldosterone during the daytime than during the night regardless of whether she received 12 mEq. of sodium during the day or 51 mEq. of sodium during the night. No correlation between the excretion of sodium and aldosterone was found. Potassium, 17-hydroxycorticosteroids, and water were also excreted in larger amounts during the daytime. A normal man whose working habits were irregular and often caused him to be awake at night excreted aldosterone irregularly and the amount excreted during the night frequently surpassed that excreted during the day. The excretion of 17-hydroxycorticosteroids and potassium, however, was always larger during the day than during the night. Another normal woman spent the second, third, fourth, and eighth days of the 9 day experimental period inactively in bed. During these days the diurnal rhythm was interrupted and sometimes reversed with a larger excretion at night. The over-all excretion of aldosterone was greater during the periods when she spent the day up and about than it was when she spent the whole 24 hours in bed. On the days when she was active, sodium was retained and there was no difference in excretion between night and day. When she spent the whole day in bed sodium was excreted predominately during the day. Throughout the study, whether she was active or not, potassium and 17-hydroxycorticoids were excreted largely during the day regardless of changes in position and activity.

A male hypophyseal dwarf excreted the same amount of aldosterone during the night and during the day despite his upright position and activity during the day. When this patient was given prednisone during the day the excretion of aldosterone during the day was larger than during the night but this effect was not observed when the patient was kept in bed during the whole 24 hours.

In all the experiments there was no correlation between the day and night cycles of sodium and of aldosterone. This is consistent with the view that alterations in the effective blood volume on standing and exercise not only influence the secretion of aldosterone but also initiate acute renal adjustments in sodium excretion. These renal mechanisms appear to be independent of aldosterone and thus their presence in Addison's disease may be explained.

DAVID M. KYDD

Vol. 1, June 7, 1958.

Matheson, N. A., and Morgan, T. N.: Diuretic Action of Chlorothiazide, p. 1195.

The administration of 2 Gm. of chlorothiazide to 10 normal male subjects caused the average urinary flow to increase 1.83 ml. per minute during the first 6 hours. Associated with this diuresis there was an increase in the excretion of bicarbonate (95.5 μEq.), chloride (245.0 μEq.), phosphorus (10.3 μEq.), sodium (306.3 μEq.), potassium (64.8 μEq.), and a decrease in the excretion of total acidity (11.4 μEq.) and ammonia (9.5 μEq.). These changes appeared within 2 hours of oral administration and continued for 12 hours. The excretion rates returned to normal during the ensuing 12 hours. Similar alterations occurred after the intravenous injection of 0.5 Gm. of the sodium salt of chlorothiazide. The changes, however, appeared more promptly, were more intense, and lasted a shorter time. The effect of chlorothiazide was compared in 3 instances to that caused by the administration of 0.5 Gm. of acetazoleamide. The latter drug caused a greater loss of water in that although the drug acted more slowly the excretion rates did not return to the control values during the second 12 hour period as they did with chlorothiazide. Acetazoleamide also caused a greater loss of

sodium and potassium during the 24 hours but did not alter the excretion rate of chloride whereas the loss of chloride following chlorothiazide was striking. The deduction is made that chlorothiazide is less potent than acetazoleamide as a carbonic anhydrase inhibitor in vivo. Hence recovery is more rapid. The loss of chloride caused by chlorothiazide suggests that another mechanism is involved in addition to whatever carbonic anhydrase inhibition activity the drug may have.

DAVID M. KYDD

Watson, W. C., Thompson, T. J., and Buchanan, J. M.: Clinical and Laboratory Studies With Chlorothiazide: An Oral Diuretic, p. 1199.

Two grams of chlorothiazide in a single oral dose was given to 22 patients with edema from various causes including 3 with pre-eclamptic toxemia of pregnancy. In all a diuresis occurred usually with an increased excretion of sodium and chloride. When the serum levels of these electrolytes are low, however, they tend to be retained and the excretion of potassium and bicarbonate increases under these circumstances. Chlorothiazide appears to be more effective in the same conditions that respond well to mersalyl. In the three instances of pre-eclamptic toxemia of pregnancy, although a diuresis was obtained, no significant fall in blood pressure occurred in these acute experiments.

DAVID M. KYDD

Hytten, F. E., and Baird, Dugald: The Development of the Nipple in Pregnancy, p. 1201.

Clinical assessments and measurements of the nipple and areola in 170 primigravidas and 104 multigravidas were made repeatedly during the prenatal period and on the first postpartum day. No antenatal preparation or treatment of the nipples was undertaken. The nipples of 59 of the 170 primigravidas were judged to have poor protraction (34.7 per cent) in early pregnancy but gradual improvement during pregnancy occurred so that by the puerperium only 13 women (7.7 per cent) had defective nipples and, of these, 3 gave up breast feeding because of difficulty. The nipples of one woman were protractile early in pregnancy but deteriorated progressively and became retractile by the puerperium. Of 75 women with second babies only 8 (10.5 per cent) had poorly protractile nipples early in pregnancy and all but 3 of these had become normally protractile by the puerperium. None of the 29 women with a third or later child had poor nipples. Therefore the assessment of nipples in early pregnancy gives limited help in predicting which women will experience difficulty with breast feeding due to inadequate nipples. The value of treatment of the nipples during pregnancy is dubious and any anatomical changes that occur are probably due to the normal physiological changes of pregnancy.

DAVID M. KYDD

The New England Journal of Medicine

Vol. 259, July 3, 1958.

Crewman, Saul, and Ward, Robert: Rubella—Demonstration of Neutralizing Antibody in Gamma Globulin and Re-evaluation of the Rubella Problem, p. 16.

The authors recommend the early administration of large doses of gamma globulin (a minimum of 20 ml. intramuscularly) for the pregnant woman who has been exposed to rubella. In support of this procedure, they present evidence for the presence of neutralizing antibody for rubella in ordinary gamma globulin, in convalescent plasma, and in convalescent gamma globulin. The authors review recent prospective studies evaluating the risk of congenital abnormality following rubella. The evidence suggests that the potential risk is increased approximately six times if rubella is acquired in the first trimester of pregnancy. The prevalence of congenital malformations has been estimated at approximately 12 per cent. The authors recommend deliberate exposure of young girls to rubella as a prophylactic measure, since a single attack of this benign childhood disease is generally followed by immunity.

DOUGLAS M. HAYNES

Correspondence

Leg Cramp Syndrome

To the Editors:

I read the article by Jerome Abrams and G. E. Aponte in the August, 1958, issue, page 432, with considerable interest, because it indirectly supports the method I have used to treat my obstetrical patients suffering with leg cramps.

First allow me to provide a little background. During World War II, part of the conditioning used for recruits during the basic training period was the field pack which was worn daily. I suppose this added weight averaged about 30 pounds. One of the frequent complaints among these young men was leg cramps in the night. Some informal investigation disclosed that this gastrocnemius spasm usually occurred when the recruit was lying on his side with the knees flexed and the feet extended, a position which allows maximum shortening of the gastrocnemius. Many found that these cramps were relieved by standing or by simply extending the knees and bringing the feet to right angles with the leg, thus stretching the gastrocnemius. Many learned to do this without completely awakening.

I have carried this over to obstetrical patients by reasoning that they had in common with the recruit an added weight that was being carried off the usual center of gravity. The reasoning may not be valid, but the treatment usually gives relief.

One way to demonstrate to the patient how the cramp occurs is to have her sharply flex the knee and extend the foot. This will produce a spasm in susceptible individuals and then the treatment can be demonstrated.

A firm bed, provided by a bed board, seems to decrease the number of cramps for some, perhaps because they tend to sleep with the legs straighter.

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INDEX TO VOLUME 76

AUTHOR INDEX*

A

ABITBOL, M. MAURICE, Rupture of the common bile duct as a cause of maternal death, 599

ABOU-SHABANAH, E. HIMMAT, BOUTSELIS, J. G., FRAJOLA, W. J., AND ULLERY, J. C., The nasal mucus smear in toxemias of pregnancy, 1248

ABRAMS, JEROME, AND APONTE, G. E., The leg cramp syndrome during pregnancy, 432

ACOSTA-SISON, H., Can primary pulmonary chorionepithelioma develop after a term pregnancy? 894

ADAMS, ELEANOR C. (*see* HERTIG, ADAMS, MCKAY, ROCK, MULLIGAN, AND MENKIN), 1025

ADAMS, FAE M. (*see* SARGENT, WESTFALL, AND ADAMS), 137

AGÜERO, OSCAR, AND LAYRISSE, MIGUEL, Megaloblastic anemia of pregnancy in Venezuela, 903

ALBERT, SALOMON N. (*see* BARTER, ALBERT, AND WINSHEL), 1062

ALDERMAN, DONALD B. (*see* GOLDENBERG AND ALDERMAN), 1204

ALLISON, H. M. (*see* BELLEW AND ALLISON), 754

ALPER, CARL (*see* SEITCHIK, SZUTKA, AND ALPER), 1151 (Re-evaluation)

ALTCHEK, A. (*see* MENDLOWITZ, ALTCHEK, AND NAFTCHI), 473

APONTE, G. E. (*see* ABRAMS AND APONTE), 432

AVENT, JAMES K. (*see* COLLINS, BURMAN, MCMAHON, AND AVENT), 363

B

BAER, HARRY (*see* PATTERSON AND BAER), 1264

BAKER, WILLIAM S., JR. (*see* LUCAS AND BAKER), 1302

— (*see* WINTER, CARMICHAEL, BARONOFSKY, AND BAKER), 572

BALIN, HOWARD, Follicular and tubal fluids in the reproductive process, 30

BALL, THOMAS L., Consultation on adrenal cortical tumor, 1358 (Clinical problems)

BANNER, EDWARD A. (*see* HERBERT, BANNER, AND WAKIM), 742

BARBER, HUGH R. K. (*see* BRUNSCHWIG AND BARBER), 199

BARBER, JOHN F., AND RATHBUN, LEWIS S., Term abdominal pregnancy with survival of mother and infant, 822

BARNES, ALLAN C. (*see* TAYLOR, BREWER, AND BARNES), 210 (Pertinent comments)

— (*see* ZUSPAN, BARNES, AND DILLHOEFER), 619

—, AND BUCKINGHAM, JOHN C., with the technical assistance of James Dillhoefer, Electrolyte balance studies with the antihormones, 955

BARONOFSKY, IVAN D. (*see* WINTER, CARMICHAEL, BARONOFSKY, AND BAKER), 572

BARTER, ROBERT H., ALBERT, SALOMON N., AND WINSHEL, ALAN W., The use of hypothermic-hypotensive technique in fulminant toxemia of pregnancy, 1062

BEECHAM, CLAYTON T., Credit for earlier statements on endometriosis and pseudopregnancy, 228 (Correspondence)

BELLEW, L. N., AND ALLISON, H. M., Experience with the Bracht method of delivery of the breech, 754

BENSON, RALPH C., AND SNEEDEN, VINTON D., Adenomyosis: a reappraisal of symptomatology, 1044

BERENBERG, ARNOLD L. (*see* BURKE, RUBIN, AND BERENBERG), 132

BIENIARZ, J., Toxemia and placenta previa, coexistence and symptomatology, reply, 227 (Correspondence)

BLATT, MARK A. (*see* SHOEMAKER, BLATT, POHL, AND GROTZINGER), 1194

BOLTON, RICHARD N., AND HUNTER, WARREN C., Adenomatoid tumors of the uterus and adnexa, 647

BOUTSELIS, J. G. (*see* ABOU-SHABANAH, BOUTSELIS, FRAJOLA, AND ULLERY), 1248

BRACK, C. BERNARD, AND GUILD, HARRIET G., Urethral obstruction in the female child, 1105

BRADFORD, W. B. (*see* WOLTZ, BRADFORD, BRADFORD, AND MCCOY), 736

BRADFORD, W. Z. (*see* WOLTZ, BRADFORD, BRADFORD, AND MCCOY), 736

BRANDT, MURRAY LAMPEL (*see* GIORLANDO AND BRANDT), 666

BREEN, J. L. (*see* RIVA AND BREEN), 192

—, Polyostotic fibrous dysplasia and pregnancy, 909

—, RIVA, H. L., AND HATCH, R. P., Hematoma of the umbilical cord, 1288

BRESLOW, LESTER (*see* JONES, MACDONALD, AND BRESLOW) 1

BREWER, JOHN I. (*see* TAYLOR, BREWER, AND BARNES), 210 (Pertinent comments)

BROWN, JAMES O. (*see* GOLUB, LANG, MENDUKE, AND BROWN), 670

BROWN, WILLIS E., AND HANISCH, E. C., A review of the aggressive management of abortion, 716

BRUNS, PAUL D. (*see* TAYLOR, BRUNS, HEPNER, AND DROSE), 983

— (*see* WEIS, BRUNS, AND TAYLOR), 340

BRUNSCHWIG, ALEXANDER, AND BARBER, HUGH R. K., Cesarean section immediately followed by radical hysterectomy and pelvic node excision, 199

BUCKINGHAM, JOHN C. (*see* BARNES AND BUCKINGHAM), 955

BUKEAVICH, ALFRED P. (*see* HODGKINSON, IGNA, AND BUKEAVICH), 279

BURCH, THOMAS A., REES, CHARLES W., AND KAYHOE, DONALD E., Laboratory and clinical studies of vaginal trichomoniasis, 658

BURKE, LOUIS, RUBIN, HAROLD W., AND BERENBERG, ARNOLD L., The significance of the unengaged vertex in a nulliparа at 38 weeks' gestation, 132

BURMAN, RICHARD G. (*see* COLLINS, BURMAN, MCMAHON, AND AVENT), 363

*July, pp. 1-234; August, pp. 235-466; September, pp. 467-698; October, pp. 699-930; November, pp. 931-1162; December, pp. 1163-1394.

C

CALDWELL, WILLIAM, Statistical validity of figures on ovarian carcinoma therapy, 464 (Correspondence)

CALIGARA, FRANCO (*see* SJÖSTEDT, ROOTH, AND CALIGARA), 1226

CARMICHAEL, DAVID B. (*see* WINTER, CARMICHAEL, BARONOFSKY, AND BAKER), 572

CARTER, BAYARD, PARKER, ROY T., THOMAS, WALTER L., CREADICK, ROBERT N., PEETE, CHARLES, CHERNY, WALTER B., AND WILLIAMS, JEAN B., The follow-up of patients with cancer of the cervix treated by radical hysterectomy and radical pelvic hymphadenectomy, 1094

CARTER, BETTINA B., AND LEWIS, A. FRANKLYN, The effects of orally administered Rh hapten, 1284

CASTELLANOS, HECTOR (*see* STURGIS AND CASTELLANOS), 1132

CAVANAGH, DENIS, Primary peritoneal pregnancy, 523

— (*see* DEMICK AND CAVANAGH), 533

— (*see* FERGUSON AND CAVANAGH), 773

CHERNY, WALTER B. (*see* CARTER, PARKER, THOMAS, CREADICK, PEETE, CHERNY, AND WILLIAMS), 1094

CHESLEY, LEON C., AND UICHANCO, LEOPOLDO, An evaluation of chlorothiazide in the treatment of edema in pregnant women, 467

CHOW, BACON F., PRYSTOWSKY, HARRY, HELLEGERS, ANDRE E., AND WONG, VERNON, Studies on the absorption of vitamin B_{12} in human pregnancy with especial reference to the effect of D-sorbitol, 91

CHRISTIAN, ROBERT T. (*see* MILLER, LUDOVICI, CHRISTIAN, AND RILEY), 1071

CLAHR, JACOB (*see* KLEIN, CLAHR, AND TAMIS), 1342

COLLINS, CONRAD G., BURMAN, RICHARD G., MCMAHON, DONALD, AND AVENT, JAMES K., Vulvectomy for benign vulvar disease: indications, technique, and results, 363

CONGER, GEORGE T., AND KEETTEL, WILLIAM C., The Manchester-Fothergill operation, its place in gynecology, 634

COPELAND, L. V., WELBURN, J. C., AND WEST, O. T., Dystocia caused by Wilms's tumor, 1329

COUNSELLER, VIRGIL S., Consultation on cytosmears, 676 (Clinical problems)

CREADICK, ROBERT N. (*see* CARTER, PARKER, THOMAS, CREADICK, PEETE, CHERNY, AND WILLIAMS). 1094

— (*see* FLOWERS, DONNELLY, CREADICK, GREENBERG, AND WELLS), 761

CULVER, GORDON J., PEREIRA, RUBENS MARCONDES, AND SEIBEL, ROY, Radiographic features of rectosigmoid endometriosis, 1176

D

DAVIS, M. EDWARD, Consultation on missed abortion, 1363 (Clinical problems)

—, AND PLOTZ, E. JÜRGEN, Hormones in human reproduction. Part II. Further investigation of steroid metabolism in human pregnancy, 939

DE ALVAREZ, RUSSELL R., Consultation on cytosmears, 677 (Clinical problems)

DECKER, WAYNE H., Early postradiation surgery for endometrial carcinoma, 20

DECOSTA, EDWIN J. (*see* REIS, DECOSTA, AND GERBIE), 1148 (Re-evaluation)

DEMICK, PAUL E., AND CAVANAGH, DENIS, Unilateral tubal twin pregnancy, 533

DENHAM, SAM WESLEY, AND FORAKER, ALVAN G., An integrated program of gynecologic research in a community hospital, 800

DENNIS, E. J. (*see* HEINS, DENNIS, AND PRATT-THOMAS), 726

DEW, RONALD, Prolonged levarterenol bitartrate (Levophed) therapy in shock following removal of a large ovarian neoplasm, 1201

DIECKMANN, WILLIAM J. (*see* FUGO AND DIECKMANN), 141

—, AND HARROD, JOHN P., Evaluation of hypotensive drug therapy in chronic hypertensive disease in pregnancy, 374

DILLHOEFER, JAMES R. (*see* BARNES AND BUCKINGHAM), 955

— (*see* ZUSPAN, BARNES, AND DILLHOEFER), 619

DOCKERTY, MALCOLM B. (*see* NELSON, DOCKERTY, PRATT, AND REMINE), 861

DONNELLY, JAMES F. (*see* FLOWERS, DONNELLY, CREADICK, GREENBERG, AND WELLS), 761

DOUGHERTY, CARY M., AND LOW, FRANK M., The fine structure of the basement membrane of the uterine cervical epithelia, 839

—, THOMPSON, WILLIAM BENBOW, JR., AND MCCALL, MILTON L., Hilus-cell and granulosa-cell tumors in the same ovary, 653

DROSE, VERA E. (*see* TAYLOR, BRUNS, HEPNER, AND DROSE), 983

E

EASTMAN, NICHOLSON J., Consultation on missed abortion, 1361 (Clinical problems)

EDWARDS, I. KEITH (*see* RIDLEY AND EDWARDS), 783

EGLI, GENE E. (*see* NEWTON AND EGLI), 103

EL-BEDRI, LAMIA, Ectopic pregnancy caused by *Schistosoma haematobium* infection of the Fallopian tube, 515

EREZ, NASID, AND YENEN, ERTUGRUL, A case of adrenogenital syndrome (adrenal pseudohermaphrodism) with subsequent pregnancy, 877

EZELL, HARRY E., JR. (*see* HOLZAEPFEL AND EZELL), 292

F

FAINSTAT, THEODORE, Cortisone-induced prolapse and inversion of the uterus in mice, 53

FEBLES ALFONZO, D. (*see* MAUTONE AND FEBLES ALFONZO), 37

FERGUSON, JAMES HENRY, Consultation on diabetes and pregnancy, 682 (Clinical problems)

—, AND CAVANAGH, DENIS, A positive cytology registry: some observations on the effect of pregnancy made with its assistance, 773

FERGUSON, ROBERT K., AND REID, DUNCAN E., Rupture of the uterus: a twenty-year report from the Boston Lying-in Hospital, 172

FIENBERG, ROBERT, Ovarian estrogenic tumors and diffuse estrogenic thecomatosis in postmenopausal colporrhagia, 851

FINNERTY, JAMES J. (*see* WINKLER, FITZPATRICK, AND FINNERTY), 1209

FITZPATRICK, JAMES G. (*see* WINKLER, FITZPATRICK, AND FINNERTY), 1209

FLETCHER, GILBERT H. (*see* RUTLEDGE AND FLETCHER), 321

FLOWERS, CHARLES E., JR., DONNELLY, JAMES F., CREADICK, ROBERT N., GREENBERG, BERNARD G., AND WELLS, H. BRADLEY, Spontaneous premature rupture of the membranes, 761

FORAKER, ALVAN G. (*see* DENHAM AND FORAKER), 800

FRAJOLA, W. J. (*see* ABOU-SHABANAH, BOUTSELIS, FRAJOLA, AND ULLERY), 1248

FRANKEL, DONALD S., Full-thickness anterior colporrhaphy for correction of urinary stress incontinence, 1185

FREDA, VINCENT J., A-B-O(H) blood group substances in the human maternal-fetal barrier and amniotic fluid, 407

FRIEDMAN, EMANUEL A., AND LITTLE, WILLIAM A., Pregnancy and gout: a case report, 913
— AND —, Toxemia and placenta previa, 919 (Pertinent comments)
FRIEDMAN, MAX M. (*see* LAPAN AND FRIEDMAN), 96
FRIEDMAN, STANLEY (*see* HOGANS AND FRIEDMAN), 188
—, AND HOGANS, CLARENCE W., Removal from the parametrium of a nail employed to induce abortion, 561
FUGO, NICHOLAS W., AND DIECKMANN, WILLIAM J., A comparison of oxytocic drugs in management of placental stage, 141
FUNARO, SERGE (*see* WEINBERG, SALZ, AND FUNARO), 542

G

GARBER, E. C., JR., AND MORRISON, R. H., Spontaneous regression of pulmonary metastases following hysterectomy for choriocarcinoma, 812
GARNET, JAMES D., Constitutional stigmas associated with endometrial carcinoma, 11
GERBIE, ALBERT B. (*see* REIS, DECOSTA, AND GERBIE), 1148 (Re-evaluation)
GILLESPIE, LUKE, Consultation on diabetes and pregnancy, 679 (Clinical problems)
GIORLANDO, STEPHEN WILLIAM, AND BRANDT, MURRAY LAMPEL, A new treatment of Trichomonas vaginitis, 666
GOLD, EDWIN M., JACOBZINER, HAROLD, AND PAKTER, JEAN, Perinatal mortality statistics, 229 (Correspondence)
GOLDENBERG, IRA S., AND ALDERMAN, DONALD B., Neurofibroma following presacral neurectomy, 1204
GOLUB, LEIB J., LANG, WARREN R., MENDUKE, HYMAN, AND BROWN, JAMES O., Therapeutic exercises for teen-age dysmenorrhea, 670
GOODWIN, WILLARD E., AND THELEN, HENRY M., Use of the looped ureteral catheter in repair of vesicovaginal fistula, 641
GORDON, CHARLES A., Relation of maternal mortality rates to all deaths associated with childbirth, 204
GORDON, LAWRENCE E., AND RUFFIN, CLARENCE L., Promethazine as an adjunct to obstetrical analgesia and sedation, 147
GRAVES, LESTER R., JR., The use of glutethimide in the labor patient, 1324
GRAY, MARY JANE, GUSBERG, SAUL B., AND GUTTMANN, RUTH, Pelvic lymph node dissection following radiotherapy, 629
GREENBERG, BERNARD G. (*see* FLOWERS, DONNELLY, CREADICK, GREENBERG, AND WELLS), 761
GREENBERG, MORRIS, JACOBZINER, HAROLD, PAKTER, JEAN, AND WEISL, BERNARD A. G., Maternal mortality in the epidemic of Asian influenza, New York City, 1957, 897
GREENBLATT, ROBERT B., A new clinical test for the efficacy of progesterone compounds, 626
GREENE, R. R. (*see* NELSON AND GREENE), 66
GROTZINGER, PAUL J. (*see* SHOEMAKER, BLATT, POHL, AND GROTZINGER), 1194
GUILD, HARRIET G. (*see* BRACK AND GUILD), 1105
GUSBERG, SAUL B. (*see* GRAY, GUSBERG, AND GUTTMANN), 629
GUTTMACHER, ALAN F. (*see* ROBERTS, SQUIRE, GUTTMACHER, AND MARSHAK), 1306
GUTTMANN, RUTH (*see* GRAY, GUSBERG, AND GUTTMANN), 629

H

HANISCH, E. C. (*see* BROWN AND HANISCH), 716
HARROD, JOHN P., JR., (*see* DIECKMANN AND HARROD), 374
HARTLEY, ARTHUR A. (*see* HUNTER, HARTLEY, TROPEA, AND ULIN), 539
HATCH, GARTH S. (*see* SPEIDEL AND HATCH), 558
HATCH, R. P. (*see* BREEN, RIVA, AND HATCH), 1288
HAYDEN, GLEN E., Progesterone-induced withdrawal bleeding as a simple physiologic test for pregnancy, 271
HAYNES, DOUGLAS M. (*see* JOHNSON AND HAYNES), 335
HEIMBACK, DENNIS P. (*see* SOTTO, HEIMBACK, AND SIEGNER), 425
HEINS, HENRY C. JR., DENNIS, E. J., AND PRATT-THOMAS, H. R., The possible role of smegma in carcinoma of the cervix, 726
HELLEGERS, ANDRE E. (*see* CHOW, PRYSTOWSKY, HELLEGERS, AND WONG), 91
HELLMAN, LOUIS M. (*see* MACRIS, HELLMAN, AND WATSON), 1214
—, SCHIFFER, MORTON A., KOHL, SCHUYLER G., AND TOLLES, WALTER E., Studies in fetal well-being: variations in fetal heart rate, 998
HENDRICKS, CHARLES H., The hemodynamics of a uterine contraction, 969
HEPNER, HAROLD J. (*see* TAYLOR, BRUNS, HEPNER, AND DROSE), 983
HERBERT, CARL M., BANNER, EDWARD A., AND WAKIM, KHALIL G., Variations in the peripheral circulation during pregnancy, 742
HERTIG, ARTHUR T., The evolution of a research program, 252
—, ADAMS, ELEANOR C., MCKAY, DONALD G., ROCK, JOHN, MULLIGAN, WILLIAM J., AND MENKIN, MIRIAM F., A thirteen-day human ovum studied histochemically, 1025
HESS, ORVAN W., Perinatal mortality statistics, reply, 229 (Correspondence)
HOBBS, KENNETH G., JR. (*see* WEEKES AND HOBBS), 1314
HODGKINSON, C. PAUL, IGNA, ELI J., AND BUKEAVICH, ALFRED P., High potency progesterone drugs and threatened abortion, 279
—, AND KELLY, WILLIAM T., Urethrovesicopubic relationships and urinary stress incontinence. IV. The uterine suspension syndrome, 1114
HOGANS, CLARENCE W. (*see* FRIEDMAN AND HOGANS), 561
—, AND FRIEDMAN, STANLEY, Rupture of the uterus due to placenta accreta at the site of a previous cornual resection, 188
HOLLENBECK, ZEPH J. R. (*see* ULLERY AND HOLLENBECK), 1083
HOLZAEPFEL, JOHN H., AND EZELL, HARRY E., JR., An evaluation of carcinoma of the cervix associated with pregnancy, 292
HUNT, ARTHUR B., Every man's legacy (presidential address), 235
HUNTER, ROBERT M., HARTLEY, ARTHUR A., TROPEA, FRANK, JR., AND ULIN, ALEXANDER W., Abdominal pregnancy followed by elimination of the placenta through the bladder, 539
HUNTER, WARREN C. (*see* BOLTON AND HUNTER), 647
HUTCHINSON, MANLY E., The South Atlantic Association of Obstetricians and Gynecologists, a twenty-year-old sectional obstetrical and gynecological society (presidential address) 699

I

IGNA, ELI J. (*see* HODGKINSON, IGNA, AND BUKEAVICH), 279
ISRAEL, S. LEON, The repudiation of low-dosage irradiation of the ovaries, 443 (Re-evaluation)

J

JACOBZINER, HAROLD (*see* GOLD, JACOBZINER, AND PAKTER), 229 (Correspondence)
— (*see* GREENBERG, JACOBZINER, PAKTER, AND WEISL), 897
JARRETT, ALVIN Q. (*see* WARE, JARRETT, AND REDA), 181
JAVERT, CARL T., Uterine polyp forceps and curettage, 61
JOHNSON, W. O., AND HAYNES, DOUGLAS M., Adenocarcinoma of the uterine fundus, 335
JONES, EDWARD GOMER, MACDONALD, IAN, AND BRESLOW, LESTER, A study of epidemiologic factors in carcinoma of the uterine cervix, 1
JONES, O. HUNTER, Pregnancy with diabetes mellitus complicated by hydramnios and loss of fetal movements, 817

K

KAPLAN, IRA I., The treatment of female sterility with x-ray therapy directed to the pituitary and ovaries, 447 (Reevaluation)
KAYHOE, DONALD E. (*see* BURCH, REES, AND KAYHOE), 658
KEATING, F. RAYMOND, JR. (*see* WILSON AND KEATING), 388
KEEGAN, JAMES (*see* MCDUFF AND KEEGAN), 1299
KEETTEL, WILLIAM C. (*see* CONGER AND KEETTEL), 634
KELLY, WILLIAM T. (*see* HODGKINSON AND KELLY), 1114
KING, JOHN A., AND MARKS, ROBERT A., Pregnancy and leprosy, 438
KIRSCHBAUM, HARRY, Hydatid degeneration of the placenta, 466 (Correspondence)
KISTNER, ROBERT W., Credit for earlier statements on endometriosis and pseudopregnancy, reply, 228 (Correspondence)
KLEIN, MILTON D., CLAHR, JACOB, AND TAMIS, ABRAHAM B., Classification and analysis of maternal deaths in Bronx County, New York, 1946-1957, 1342
KOHL, SCHUYLER G. (*see* HELLMAN SCHIFFER, KOHL, AND TOLLES), 998
KOREN, ZEV (*see* SALZBERGER AND KOREN), 1275
KOTTMEIER, H. L., Current treatment of carcinoma of cervix, 243
KREIS, DAVID J., AND MILLER, ROBERT T., Interlocked twins, 1334
KRIEGER, JAMES S., AND MCCORMACK, LAWRENCE J., The indications for conservative therapy for intraepithelial carcinoma of the uterine cervix, 312

L

LACK, ARTHUR (*see* MOYERS AND LACK), 518
LAMOTTA, RUDOLPH V. (*see* WETSTONE, LAMOTTA, MIDDLEBROOK, TENNANT, AND WHITE), 480
LANG, WARREN R. (*see* GOLUB, LANG, MENDUKE, AND BROWN), 670
LAPAN, BERNARD, AND FRIEDMAN, MAX M., Blood studies in normal pregnancy and the newborn: the effects of iron and calcium administration, 96
LATOUR, J. P. A., Statistical validity of figures on ovarian carcinoma therapy (reply), 465 (Correspondence)
LAWRENCE, GEORGE J., JR. (*see* PENNISI, LAWRENCE, AND VEPROVSKY), 1294
LAYRISSE, MIGUEL (*see* AGÜERO AND LAYRISSE), 903
LEVENTHAL, MICHAEL L., The Stein-Leventhal syndrome, 825
LEWIS, A. FRANKLYN (*see* CARTER AND LEWIS), 1285
LITTLE, WILLIAM A. (*see* FRIEDMAN AND LITTLE), 913
— (*see* FRIEDMAN AND LITTLE), 919 (Pertinent comments)
LOW, FRANK M. (*see* DOUGHERTY AND LOW), 839
LUCAS, WILLIAM E., AND BAKER, WILLIAM S., JR., Hematoma of the rectus abdominis muscle simulating rupture of the pregnant uterus, 1302
LUDOVICI, PETER P. (*see* MILLER, LUDOVICI, CHRISTIAN, AND RILEY), 1071
LUND, CURTIS J., AND SISSON, THOMAS R. C., Blood volume and anemia of mother and baby, 1013

M

MCCALL, MILTON L. (*see* DOUGHERTY, THOMPSON, AND MCCALL), 653
MCCORMACK, LAWRENCE J. (*see* KRIEGER AND MCCORMACK), 312
MCCOY, JOSEPH B., JR. (*see* WOLTZ, BRADFORD, BRADFORD, AND MCCOY), 736
MACDONALD, IAN (*see* JONES, MACDONALD, AND BRESLOW), 1
MCDUFF, HENRY C., JR., AND KEEGAN, JAMES, Postpartum inversion of a unicornuate uterus, 1299
MCKAY, DONALD G. (*see* HERTIG, ADAMS, MCKAY, ROCK, MULLIGAN, AND MENKIN), 1025
MACKEY, WILLIAM F. (*see* REINBERGER AND MACKEY), 288
MCMAHON, DONALD (*see* COLLINS, BURMAN, MCMAHON, AND AVENT), 363
MACRIS, NICHOLAS T., HELLMAN, LOUIS M., AND WATSON, R. J., The transmission of transfused sickle-trait cells from mother to fetus, 1214
MCSWEENEY, DANIEL J., Fetal weight estimation, 1279
MADDI, FRANCES V. (*see* PAPANICOLAOU AND MADDI), 601
MARKS, ROBERT A. (*see* KING AND MARKS), 438
MARSHAK, RICHARD (*see* ROBERTS, SQUIRE, GUTTMACHER, AND MARSHAK), 1306
MAUTONE, JOSÉ A., AND FEBLES ALFONZO, D., Pseudotubercular granulations of the uterine tube, 37
MAY, HARVEY C., Carcinoma in situ of the vagina subsequent to hysterectomy for carcinoma in situ of the cervix, 807
MENDLOWITZ, M., ALTCHEK, A., AND NAFTCHI, N., The work and force of digital vasoconstriction in normotensive and hypertensive pregnant women, 473
MENDUKE, HYMAN (*see* GOLUB, LANG, MENDUKE, AND BROWN), 670
MENKIN, MIRIAM F. (*see* HERTIG, ADAMS, MCKAY, ROCK, MULLIGAN, AND MENKIN), 1025
MIDDLEBROOK, LOUIS (*see* WETSTONE, LAMOTTA, MIDDLEBROOK, TENNANT, AND WHITE), 480
MILLER, NORMAN F., LUDOVICI, PETER P., CHRISTIAN, ROBERT T., AND RILEY, GARDNER M., Irradiation sensitivity of cervix cancer, 1071
MILLER, ROBERT T. (*see* KREIS AND MILLER), 1334
MILLER, THEODORE R., Sarcoma botryoides, 1172
MONTGOMERY, THADDEUS L., Physiologic considerations in labor and the puerperium, 706
MORRISON, R. H. (*see* GARBER AND MORRISON), 812
MOYERS, EMMET C., JR., AND LACK, ARTHUR, Primary ovarian pregnancy, 518
MULLA, NEJDAT, Labor following severe thermal burns, 1338
MULLIGAN, WILLIAM J. (*see* HERTIG, ADAMS, MCKAY, ROCK, MULLIGAN, AND MENKIN), 1025

N

NAFTCHI, N. (*see* MENDLOWITZ, ALTCHEK, AND NAFTCHI), 473
NELSON, GUNARD A., DOCKERTY, MALCOLM B., PRATT, JOSEPH HYDE, AND REMINE, WILLIAM H., Malignant lymphoma involving the ovaries, 861
NELSON, W. W., AND GREENE, R. R., Some observations on the histology of the human ovary during pregnancy, 66
NEWTON, MICHAEL, AND EGLI, GENE E., The effect of intranasal administration of oxytocin on the let-down of milk in lactating women, 103
NEWTON, WILLIAM A., JR. (*see* WILLIAMS, ULLERY, SHAFFER, AND NEWTON), 305

O

OPPENHEIM, ABRAHAM (*see* SOLOMON, PANAGOTOPOULOS, AND OPPENHEIM), 56

P

PAKTER, JEAN (*see* GOLD, JACOBZINER, AND PAKTER), 229 (Correspondence)
— (*see* GREENBERG, JACOBZINER, PAKTER, AND WEISL), 897
PANAGOTOPOULOS, PAUL (*see* SOLOMON, PANAGOTOPOULOS, AND OPPENHEIM), 56
PAPANICOLAOU, GEORGE N., AND MADDI, FRANCES V., Observations on the behavior of human endometrial cells in tissue culture, 601
PARKER, ROY T. (*see* CARTER, PARKER, THOMAS, CREADICK, PEETE, CHERNY, AND WILLIAMS), 1094
PATTERSON, RUSHTON E., AND BAER, HARRY, Evaluation of a diuretic substance in the management of mild pre-eclampsia, 1264
PEDOWITZ, PAUL, AND PERELL, ARTHUR, Rupture of the uterus, 161
—, AND SHLEVIN, EDMUND L., Diabetes mellitus and pregnancy (1932-1957), 417
PEETE, CHARLES (*see* CARTER, PARKER, THOMAS, CREADICK, PEETE, CHERNY, AND WILLIAMS), 1094
PENNISI, JOSEPH A., LAWRENCE, GEORGE J., JR., AND VEPROVSKY, EDWARD C., Bacteremic shock associated with Pseudomonas sepsis and stillbirth, 1294
PEREIRA, RUBENS MARCONDES (*see* CULVER, PEREIRA, AND SEIBEL), 1176
PERELL, ARTHUR (*see* PEDOWITZ AND PERELL), 161
PLOTZ, E. JÜRGEN (*see* DAVIS AND PLOTZ), 939
POHL, CHARLES E. (*see* SHOEMAKER, BLATT, POHL, AND GROTZINGER), 1194
POLIAKOFF, SAMUEL R., Pregnancy in the young primigravida, 746
PRATT, JOSEPH HYDE (*see* NELSON, DOCKERTY, PRATT, AND REMINE), 861
PRATT-THOMAS, H. R. (*see* HEINS, DENNIS, AND PRATT-THOMAS), 726
PRITCHARD, JACK A., Abruptio placentae and hypofibrinogenemia, 347
PRYSTOWSKY, HARRY (*see* CHOW, PRYSTOWSKY, HELLEGERS, AND WONG), 91

R

RAHILLY, JOHN (*see* STURGIS AND CASTELANOS), 1132
RATHBUN, LEWIS S. (*see* BARBER AND RATHBUN), 822
REDA, FRANK A. (*see* WARE, JARRETT, AND REDA), 181
REEL, PHILIP J., Malignant Brenner tumor of the ovary, 872
REES, CHARLES W. (*see* BURCH, REES, AND KAYHOE), 658
REID, DUNCAN E. (*see* FERGUSON AND REID), 172
REINBERGER, JAMES R., AND MACKEY, WILLIAM F., Cardiovascular reactions to Pitocin, 288
REIS, RALPH A., DECOSTA, EDWIN J., AND GERBIE, ALBERT B., Pregnancy in the diabetic woman, 1148 (Re-evaluation)
REMINE, WILLIAM H. (*see* NELSON, DOCKERTY, PRATT, AND REMINE), 861
RICHARDSON, A. CULLEN, AND WILLIAMS, GEORGE A., Topical androgenic hormones in vulvar kraurosis-leukoplakia syndrome, 791
RIDLEY, JOHN H., AND EDWARDS, I. KEITH, Experimental endometriosis in the human, 783
RILEY, GARDNER M. (*see* MILLER, LUDOVICI, CHRISTIAN, AND RILEY), 1071
RIVA, H. L. (*see* BREEN AND RIVA), 909
— (*see* BREEN, RIVA, AND HATCH), 1288
—, AND BREEN, J. L., An analysis of one hundred vaginal deliveries following cesarean section, 192
—, AND STAPLES, P. P., Knee rest apparatus for the culdoscopy patient, 63
ROBERTS, LEONARD M., SQUIRE, JACK J., GUTTMACHER, ALAN F., AND MARSHAK, RICHARD, Intrapartum lateral x-ray in the conduct of dystocic labors, 1306
ROCK, JOHN (*see* HERTIG, ADAMS, MCKAY, ROCK, MULLIGAN, AND MENKIN), 1025
ROOTH, GÖSTA (*see* SJÖSTEDT, ROOTH, AND CALIGARA), 1226
ROTTER, CARL W., Surgical correction of congenital atresia of the cervix, 643
RUBIN, ALAN, Studies in human reproduction. II. The influence of diabetes mellitus in men upon reproduction, 25
RUBIN, HAROLD W. (*see* BURKE, RUBIN, AND BERENBERG), 132
RUFFIN, CLARENCE L. (*see* GORDON AND RUFFIN), 147
RUTLEDGE, FELIX N., AND FLETCHER, GILBERT H., Transperitoneal pelvic lymphadenectomy following supervoltage irradiation for squamous-cell carcinoma of the cervix, 321

S

SALERNO, LOUIS J., Psychophysiologic aspects of the toxemias of pregnancy, 1268
SALZ, MICHEL (*see* WEINBERG, SALZ, AND FUNARO), 542
SALZBERGER, MACCABI, AND KOREN, ZEV, Pregnancy associated with thrombocytopenic purpura and eclampsia, 1275
SANDLER, MELVIN J., Torsion of Fallopian tube following tubal ligation, 41
SARGENT, C. W., WESTFALL, C. H. P., AND ADAMS, FAE M., The obstetric risk of the Japanese woman with a Caucasian husband, 137
SCHELPERT, JOHN W., III, Hydatidiform mole, 883
SCHIFFER, MORTON A. (*see* HELLMAN, SCHIFFER, KOHL, AND TOLLES), 998
SCHOCHET, SYDNEY S., (*see* ZLATNIK, WELD, SCHOCHET, AND SCHOCHET), 536
SCHOCHET, SYDNEY S., JR. (*see* ZLATNIK, WELD, SCHOCHET, AND SCHOCHET), 536
SECOR, HAROLD E., Leg cramp syndrome, 1372 (Correspondence)
SEDLIS, ALEXANDER (*see* STONE, SEDLIS, AND ZUCKERMAN), 544
SEIBEL, ROY (*see* CULVER, PEREIRA, AND SEIBEL), 1176
SEITCHIK, JOSEPH, SZUTKA, ANTON, AND ALPER, CARL, Further studies on the metabolism of N^{15}-labeled uric acid in normal and toxemic pregnant women, 1151 (Re-evaluation)
SHAFFER, THOMAS E. (*see* WILLIAMS, ULLERY, SHAFFER, AND NEWTON), 305
SHANKLIN, R. D., Toxemia and placenta previa, coexistence and symptomatology, 227 (Correspondence)
SHARP, MAHLON S., Acute poliomyelitis in private obstetrical practice, 299
SHETTLES, LANDRUM B., The living human ovum, 398
SHLEVIN, EDMUND L. (*see* PEDOWITZ AND SHLEVIN), 417

SHOEMAKER, WILLIAM C., BLATT, MARK A., POHL, CHARLES E., AND GROTZINGER, PAUL J., Reconstruction of the vagina of dogs with reversed seromuscular grafts, 1194
SIEGNER, ALLAN W. (*see* SOTTO, HEIMBACK, AND SIEGNER), 425
SISSON, THOMAS R. C. (*see* LUND AND SISSON), 1013
SJÖSTEDT, SVEN, ROOTH, GÖSTA, AND CALIGARA, FRANCO, The oxygen tension of the amniotic fluid, 1226
SNEEDEN, VINTON D. (*see* BENSON AND SNEEDEN), 1044
SOELLING, WARNER M., Appendicitis during pregnancy, 1291
SOLOMON, CYRIL, PANAGOTOPOULOS, PAUL, AND OPPENHEIM, ABRAHAM, The use of urinary sediment as an aid in endocrinological disorders in the female, 56
SOTTO, LUCIANO S. J., HEIMBACK, DENNIS P., AND SIEGNER, ALLAN W., Unsuspected "prediabetic state" and pregnancy, 425
SPARKMAN, ROBERT S., Rupture of the spleen in pregnancy, 587
SPEERT, HAROLD, The uterine decidua in ectopic pregnancy: its natural history and some biologic interpretations, 491
SPEIDEL, THOMAS H., AND HATCH, GARTH S., The case of the missing catheter, 558
SQUIRE, JACK J. (*see* ROBERTS, SQUIRE, GUTTMACHER, AND MARSHAK), 1306
STAPLES, P. P. (*see* RIVA AND STAPLES), 63
STEER, CHARLES M., Fetal wastage at the Sloane Hospital for Women, 563
—, X-ray pelvimetry and the outcome of labor, 118
STEFFAN, LLOYD J. (*see* WEISSE, WATSON, AND STEFFAN), 1207
STEIN, WILLIAM W., An evaluation of a combination of testosterone enanthate with estradiol valerate (Deladumone), for the inhibition of lactation, 108
STONE, MARTIN L., SEDLIS, ALEXANDER, AND ZUCKERMAN, MARVIN, Relaxin—a critical evaluation, 544
STURGIS, SOMERS H., AND CASTELLANOS, HECTOR, with the technical assistance of JOHN RAHILLY, Ovarian homografts in the primate: experience with Millipore filter chambers, 1132
SZUTKA, ANTON (*see* SEITCHIK, SZUTKA, AND ALPER), 1151 (Re-evaluation)

T

TAMIS, ABRAHAM B. (*see* KLEIN, CLAHR, AND TAMIS), 1342
TAYLOR, CLIFFORD R., The intrauterine bougie and Voorhees bag today, 553
TAYLOR, E. STEWART, Consultation on adrenal cortical tumor, 1357 (Clinical problems)
— (*see* WEIS, BRUNS, AND TAYLOR), 340
—, BRUNS, PAUL D., HEPNER, HAROLD J., AND DROSE, VERA E., Measurements of placental function, 983
TAYLOR, HOWARD C., JR., Competition and cooperation (presidential address), 931
—, BREWER, JOHN I., AND BARNES, ALLAN C., Announcement of department of current opinion, 210 (Pertinent comments)
TAYLOR, HOWARD P., Conservation of postpartum nurses' time—bedside self-medication and patient control of visiting, 215 (Pertinent comments)
TENNANT, ROBERT (*see* WETSTONE, LAMOTTA, MIDDLEBROOK, TENNANT, AND WHITE), 480
THELEN, HENRY M. (*see* GOODWIN AND THELEN), 641
THOMAS, WALTER L. (*see* CARTER, PARKER, THOMAS, CREADICK, PEETE, CHERNY, AND WILLIAMS), 1094
THOMPSON, WILLIAM BENBOW, JR. (*see* DOUGHERTY, THOMPSON, AND MCCALL), 653
TOLLES, WALTER E. (*see* HELLMAN, SCHIFFER, KOHL, AND TOLLES), 998
TOPOLANSKI-SIERRA, RICARDO, Pelvic phlebography, 44
TROPEA, FRANK, JR. (*see* HUNTER, HARTLEY, TROPEA, AND ULIN), 539

U

UHMA, C., Excision biopsy of cervix, 465 (Correspondence)
UICHANCO, LEOPOLDO (*see* CHESLEY AND UICHANCO), 467
ULIN, ALEXANDER W. (*see* HUNTER, HARTLEY, TROPEA, AND ULIN), 539
ULLERY, JOHN C. (*see* ABOU-SHABANAH, BOUTSELIS, FRAJOLA, AND ULLERY), 1248
— (*see* WILLIAMS, ULLERY, SHAFFER, AND NEWTON), 305
—, AND HOLLENBECK, ZEPH J. R., Early diagnosis and treatment in a cancer survey program, 1083

V

VEPROVSKY, EDWARD C. (*see* PENNISI, LAWRENCE, AND VEPROVSKY), 1294

W

WAKIM, KHALIL G. (*see* HERBERT, BANNER, AND WAKIM), 742
WALKER, JAMES, Prolonged pregnancy syndrome, 1231
WALL, ROSCOE L., JR., Didelphic uterus with carcinoma in situ in both cervices, 803
WARE, H. HUDNALL, JR., JARRETT, ALVIN Q., AND REDA, FRANK A., Rupture of the gravid uterus, 181
WATSON, MARK (*see* WEISSE, WATSON, AND STEFFAN), 1207
WATSON, R. J. (*see* MACRIS, HELLMAN, AND WATSON), 1214
WEEKES, LEROY R., AND HOBBS, KENNETH G., JR., Dystocia and occipitoposterior, 1314
WEINBERG, MILTON S., SALZ, MICHEL, AND FUNARO, SERGE, A case of intra-abdominal pregnancy with follow-up tests for disappearance of placental activity, 542
WEIS, EDMUND B., JR., BRUNS, PAUL D., AND TAYLOR, E. STEWART, A comparative study of the disappearance of radioactive sodium from human uterine muscle in normal and abnormal pregnancy, 340
WEISL, BERNARD A. G. (*see* GREENBERG, JACOBZINER, PAKTER, AND WEISL), 897
WEISSE, HARRIS A., WATSON, MARK, AND STEFFAN, LLOYD J., Traumatic rupture of the apex of the vagina twenty months following abdominal hysterectomy, 1207
WELBURN, J. C. (*see* COPELAND, WELBURN, AND WEST), 1329
WELD, S. L. (*see* ZLATNIK, WELD, SCHOCHET, AND SCHOCHET), 536
WELLS, H. BRADLEY (*see* FLOWERS, DONNELLY, CREADICK, GREENBERG, AND WELLS), 761
WEST, O. T. (*see* COPELAND, WELBURN, AND WEST), 1329
WESTFALL, C. H. P. (*see* SARGENT, WESTFALL, AND ADAMS), 137
WETSTONE, HOWARD J., LAMOTTA, RUDOLPH V., MIDDLEBROOK, LOUIS, TENNANT, ROBERT, AND WHITE, BENJAMIN V., Studies of cholinesterase activity. IV. Liver function tests in pregnancy; values of certain standard liver function tests in normal pregnancy, 480
WHEATLEY, ROBERT E., Prolonged retention of a dead fetus, 1283
WHITE, BENJAMIN V. (*see* WETSTONE, LAMOTTA, MIDDLEBROOK, TENNANT, AND WHITE), 480

WILLIAMS, GEORGE A. (*see* RICHARDSON AND WILLIAMS), 791
WILLIAMS, JAMES HUTCHISON, ULLERY, JOHN C., SHAFFER, THOMAS E., AND NEWTON, WILLIAM A., JR., Dynamic investigation of perinatal mortality, 305
WILLIAMS, JEAN B. (*see* CARTER, PARKER, THOMAS, CREADICK, PEETE, CHERNY, AND WILLIAMS), 1094
WILSON, ROBERT B., AND KEATING, F. RAYMOND, JR., Pregnancy following treatment of congenital adrenal hyperplasia with cortisone, 388
WINKELSTEIN, L. B., Routine hypnosis for obstetrical delivery, 152
WINKLER, EDWARD G., FITZPATRICK, JAMES G., AND FINNERTY, JAMES J., The permeability of the rabbit placenta to homologous albumin, 1209
WINSHEL, ALAN W. (*see* BARTER, ALBERT, AND WINSHEL), 1062
WINTER, WILLIAM R., CARMICHAEL, DAVID B., BARONOFSKY, IVAN D., AND BAKER, WILLIAM S., JR., Cardiac surgery associated with pregnancy, 572
WIRTSCHAFTER, ZOLTON T., Free amino acids in human amniotic fluid, fetal and maternal serum, 1219
WOLFE, LOUIS A., Colpomicroscopy: its value in the microscopic examination of the uterine cervical epithelium in vivo, 1163
WOLTZ, JOHN H. E., BRADFORD, W. Z., BRADFORD, W. B., AND MCCOY, JOSEPH B., JR., Complications of hysterosalpingography, 736
WONG, VERNON (*see* CHOW, PRYSTOWSKY, HELLEGERS, AND WONG), 91

Y

YENEN, ERTUGRUL (*see* EREZ AND YENEN), 877

Z

ZLATNIK, A. P., WELD, S. L., SCHOCHET, SYDNEY S., JR., AND SCHOCHET, SYDNEY S., Combined tubal and intrauterine pregnancy, 536
ZUCKERMAN, MARVIN (*see* STONE, SEDLIS, AND ZUCKERMAN), 544
ZUSPAN, FREDERICK P., BARNES, ALLAN C., AND DILLHOEFER, JAMES R., The urinary excretion of antidiuretic substances by the obstetric and gynecologic patient, 619

SUBJECT INDEX*

A

Abdominal pregnancy (*see* Pregnancy, abdominal)
ABO blood groups in Ireland, distribution (Hackett and Dawson), 691 (Abst.)
A-B-O hemolytic disease, possible mechanism (Freda), 414
A-B-O(H) blood group substances in maternal-fetal barrier and amniotic fluid (Freda), 407
Abortion, aggressive management (Brown and Hanisch), 716
  history (Brown and Hanisch), 716
  incidence in wives of diabetic men (Rubin), 28
  induced, 558-562
  legal, in Sweden (Arén) 689 (Abst.)
  missed, consultation (Eastman and Davis), 1361 (Clinical problems)
  nail to induce, removal from parametrium (Friedman and Hogans), 561
  spontaneous, rates (Steer), 564
  therapeutic, rates (Steer), 565
  threatened, high potency progesterone drugs and (Hodgkinson, Igna, and Bukeavich), 279
  in the United States (Calderone), 1156 (B. rev.)
Abruptio placentae and hypofibrinogenemia (Pritchard), 347
Abstracts, 220, 456, 689, 923, 1160, 1366
Acidosis, maternal, ammonium chloride induced, effect on fetus (Kaiser and Goodlin), 924 (Abst.)
Acids, amino, free, in amniotic fluid and serum (Wirtschafter), 1219
Adenocarcinoma (*see also* Carcinoma)
  of adrenal cortex, consultation (Taylor and Ball), 1357 (Clinical problems)
  of cervix, irradiation sensitivity (Miller et al.), 1078
    salvage (Carter et al.), 1094
  of endometrium, tissue culture (Papanicolaou and Maddi), 613
  of uterine fundus (Johnson and Haynes), 335
Adenoma, cortical, case (Erez and Yenen), 877
  hilus-cell, of ovary (Dougherty, Thompson, and McCall), 656
Adenomatoid tumors of uterus and adnexa (Bolton and Hunter), 647
Adenomyosis, symptomatology (Benson and Sneeden), 1044
Adnexa, adenomatoid tumors of (Bolton and Hunter), 647
Adrenal cortical tumor, consultation (Taylor and Ball), 1357 (Clinical problems)
  gland, role in Stein-Leventhal syndrome (Leventhal), 831
  hyperplasia, congenital, pregnancy following treatment with cortisone (Wilson and Keating), 388
  pseudohermaphrodism with later pregnancy (Erez and Yenen), 877
Adrenogenital syndrome, congenital, treatment with cortisone, pregnancy following (Wilson and Keating), 388
    with later pregnancy (Erez and Yenen), 877
Albumin, homologous, permeability of rabbit placenta to (Winkler, Fitzpatrick, and Finnerty), 1209
Aldosterone antagonist, effects on electrolyte balance (Barnes and Buckingham), 958
  secretion, influence of position and activity on (Muller, Manning, and Riondel), 1370 (Abst.)
Alkaline phosphatase, serum, in pregnancy (Wetstone et al.), 482
Allergy in pediatric practice (Sherman and Kessler), 219 (B. rev.)
Amenorrhea, irradiation of ovaries for, repudiation (Israel), 443 (Re-evaluation)
  and pregnancy, differentiation by progesterone induced withdrawal bleeding (Hayden), 271
American Board of Obstetrics and Gynecology, 226, 466, 1162 (Items)
    certifications, 694 (Item)
American Gynecological Society, transactions of eighty-first annual meeting, 931
American Society for Study of Sterility, grants-in-aid, 930 (Item)
Amino acids, free, in amniotic fluid and serum (Wirtschafter), 1219
Ammonium chloride induced maternal acidosis, effect on fetus (Kaiser and Goodlin), 924 (Abst.)
Amnion cells, proliferation in submerged culture (Davis, Glover, and McLimans), 462 (Abst.)
  placenta and, function, 1209-1230
Amniotic fluid, A-B-O(H) blood group substances in (Freda), 407
  free amino acids in (Wirtschafter), 1219
  oxygen tension (Sjöstedt, Rooth, and Caligara), 1226
Analgesia and anesthesia in labor (Montgomery), 707
  and sedation, promethazine as adjunct (Gordon and Ruffin), 147
Androgenic hormones, topical, in vulvar kraurosis-leukoplakia (Richardson and Williams), 791
Androgens, production by hilus cells of ovary (Dougherty, Thompson, and McCall), 657
Anemia, blood volume and, of mother and baby (Lund and Sisson), 1013
  megaloblastic, of pregnancy, in Venezuela (Agüero and Layrisse), 903
Anesthesia, cause of maternal death (Klein, Clahr, and Tamis), 1348
  in labor (Montgomery), 707
Announcement by Editors, 210
Anomalies, genital, hermaphroditism, and related endocrine disorders (Jones and Scott), 921 (B. rev.)
  of uterine action and treatment (Kaern), 923 (Abst.)
Anoxia, newborns with, behavior test performance (Graham et al.), 46 (Abst).
Antidiuretic substances, urinary excretion (Zuspan, Barnes, and Dilihoefer), 619
Antihormones, electrolyte balance studies with (Barnes and Buckingham), 955
Aorta, coarctation, pregnancy and (Goodwin), 220 (Abst.)
    in pregnancy (Winter et al.), 582
Appendicitis in pregnancy (Soelling), 1291
Apresoline in hypertensive disease in pregnancy (Dieckmann and Harrod), 377

*July, pp. 1-234; August, pp. 235-466; September, pp. 467-698; October, pp. 699-930; November, pp. 931-1162; December, pp. 1163-1394.

Arterial pressure and flow in digital circulation (Mendlowitz, Altchek, and Naftchi), 473
Asian influenza epidemic, maternal mortality, in New York City, 1957 (Greenberg et al.), 897
Asphyxia, protracted, fetal and neonatal (Bullough), 927 (Abst.)
Atresia of cervix, congenital; surgical correction (Rotter), 643
Aureomycin, results in trichomoniasis (Burch, Rees, and Kayhoe), 664

B

Baby and mother, protection from hospital infection (Montgomery), 712
placenta, and cord, relationship (Montgomery), 710
Bacteremic shock with Pseudomonas sepsis and stillbirth (Pennisi, Lawrence, and Veprovsky), 1294
Bacterial toxins in treatment of tumors, effects on normal and sarcoma 37-bearing mice (Donnelly, Havas, and Goresbeck), 460 (Abst.)
Bacteriologic content of smegma (Heins, Dennis, and Pratt-Thomas), 728
Bag, Voorhees, and intrauterine bougie, present status (Taylor), 553
Basement membrane of cervical epithelia, fine structure (Dougherty and Low), 839
Behavior test performance of newborns with anoxia (Graham et al.), 461 (Abst.)
Betatron, 22 Mev, irradiation technique with (Rutledge and Fletcher), 325
Bile duct, common, rupture, cause of maternal death (Abitbol), 599
Bilharziasis, ectopic pregnancy resulting from (El-Bedri), 516
Bilirubin, serum, in pregnancy (Wetstone et al.), 484
Billig exercises for dysmenorrhea (Golub et al.), 670
Biologic interpretations of uterine decidua in ectopic pregnancy (Speert), 491
Biopsy, excision, of cervix (Uhma), 465 (Correspondence)
Bladder, elimination of placenta through (Hunter et al.), 539
Bleeding, adenomyosis as cause (Benson and Sneeden), 1054
rectal, symptom of rectosigmoid endometriosis (Culver, Pereira, and Seibel), 1177
vaginal, postmenopausal, problem of (Fienberg), 851
withdrawal, progesterone-induced, as test for pregnancy (Hayden), 271
Blood, disappearance of progesterone from (Davis and Plotz), 945
group substances, A-B-O(H), in maternal-fetal barrier and amniotic fluid (Freda), 407
groups, ABO and simple Rh, in Ireland, distribution (Hackett and Dawson), 691 (Abst.)
hormones in (Wolstenholme and Miller), 455 (B. rev.)
in peritoneal cavity, fate (Pritchard and Adams), 224 (Abst.)
pressure changes during therapy for hypertensive disease in pregnancy (Dieckmann and Harrod), 379
during uterine contraction (Hendricks), 974
studies in pregnancy and newborn (Lapan and Friedman), 96
transfusions, role in treatment of hypofibrinogenemia (Pritchard), 359
volume and anemia of mother and baby (Lund and Sisson), 1013
Book reviews, 218, 454, 686, 921, 1156, 1364
Books received, 219, 456, 689, 922, 1159, 1366
Bougie, intrauterine, and Voorhees bag, present status (Taylor), 553
Bracht method of delivery of breech (Bellew and Allison), 754
Braxorone, progestational activity (Greenblatt), 626
Breast cancer (*see* Carcinoma of breast)
feeding, relation to let-down reflex (Newton and Egli), 103
Breech, Bracht method of delivery (Bellew and Allison), 754
Brenner tumor, malignant, of ovary (Reel), 872
Bronx County, New York, maternal deaths in, 1946-1957 (Klein, Clahr, and Tamis), 1342
Burns, thermal, severe, labor after (Mulla), 1338

C

Calcium administration, in pregnancy and newborn (Lapan and Friedman), 96
metabolism, relationship of leg cramp syndrome to (Abrams and Aponte), 432
Canadian Society for Study of Fertility, 698 (Abst.)
Cancer (*see* Carcinoma)
Capillary fragility from ovarian deficiency, hemorrhagic diathesis due to (Wells), 927 (Abst.)
Carcinoma (*see also* Adenocarcinoma, Carcinosarcoma, Choriocarcinoma, Chorionepithelioma, Sarcoma, Tumor, Tumors)
of breast, endocrine aspects, 688 (B. rev.)
hypophysectomy in pregnant patient with (Little et al.), 1161 (Abst.)
surgically treated, mortality and survival (Berkson et al.), 462 (Abst.)
of cervix, adenocarcinoma, salvage (Carter et al.), 1094
circumcision and (Jones, Macdonald, and Breslow), 4
colpomicroscopic observation (Wolfe), 1169
current treatment (Kottmeier), 243
epidemiologic factors (Jones, Macdonald, and Breslow), 1
estrogens, excretion, and (Jones, Macdonald, and Breslow), 9
intraepithelial, conservative therapy (Krieger and McCormack), 312
irradiation sensitivity (Miller et al.), 1071
treatment (Kottmeier), 243
nutritional factors (Jones, Macdonald, and Breslow), 4
pelvic lymphadenectomy after radiotherapy for (Gray, Gusberg, and Guttmann), 629
in pregnancy (Holzaepfel and Ezell), 292
cesarean section and radical operation for (Brunschwig and Barber), 199
psychophysical stress and (Jones, Macdonald, and Breslow), 8
recurrent, management (Kottmeier), 245
role of smegma in (Heins, Dennis and Pratt-Thomas), 726
sexual practices and (Jones, Macdonald, and Breslow), 5
in situ, conservative therapy (Krieger and McCormack), 312
socioeconomic factors (Jones, Macdonald, and Breslow), 4
squamous-cell, lymphadenectomy after supervoltage irradiation for (Rutledge and Fletcher), 321
salvage (Carter et al.), 1094
treated by radical surgery (Carter et al.), 1094
of colon, endometriosis differentiated from (Culver, Pereira, and Seibel), 1177
of corpus uteri, radical operation for (Schwartz and Brunschwig), 225 (Abst.)
of endometrium (Johnson and Haynes), 335
and bilateral polycystic ovaries (Leventhal), 836
constitutional stigmas (Garnet), 11
diabetes mellitus and (Garnet), 11
early postradiation surgery for (Decker), 20

Carcinoma—Cont'd
and irradiation (Kaplan), 450 (Re-evaluation)
of ovary, statistical validity of figures on (Caldwell and Latour), 464 (Correspondence)
in situ of both cervices of didelphic uterus (Wall), 803
of cervix, conservative therapy (Krieger and McCormack), 312
diagnosed by cytosmear (Counseller and de Alvarez), 675 (Clinical problems)
hysterectomy for, carcinoma in situ of vagina after (May), 807
incidence in Columbus survey (Ullery and Hollenbeck), 1090
of vagina after hysterectomy for carcinoma in situ of cervix (May), 807
squamous-cell, of cervix (*see* Carcinoma of cervix, squamous-cell)
survey program, diagnosis and treatment in (Ullery and Hollenbeck), 1083
of uterus, *Annual Report on Results of Treatment*, importance (Kottmeier), 243
Carcinosarcoma of endometrium, tissue culture (Papanicolaou and Maddi), 614
Cardiac arrhythmias with hypothermia (Barter, Albert, and Winshel), 1066
disease, leading cause of maternal death (Winter et al.), 572
in pregnancy (Masani), 693 (Abst.)
rheumatic, hazard in epidemic of Asian influenza (Greenberg et al.), 901
diseases complicating pregnancy (Bose), 692 (Abst.)
output during uterine contraction (Hendricks), 972
surgery in pregnancy (Winter et al.), 572
Cardiovascular reactions to Pitocin (Reinberger and Mackey), 288
Catheter, missing, case of (Speidel and Hatch), 559
ureteral, looped, in vesicovaginal fistula repair (Goodwin and Thelen), 641
Caucasian husband, obstetric risk of Japanese woman with (Sargent, Westfall, and Adams), 137
Cells, endometrial, in tissue culture, behavior (Papanicolaou and Maddi), 601
Central Association of Obstetricians and Gynecologists, transactions of twenty-fifth annual meeting, 235
Cephalin-cholesterol flocculation in pregnancy (Wetstone et al.), 485
Cerebral palsy, twins and (Gingras et al.), 1367 (Abst.)
Cervical epithelia, fine structure of basement membrane (Dougherty and Low), 839
epithelium, colpomicroscopic examination (Wolfe), 1163
pregnancy (*see* Pregnancy, cervical)
tumors, 1163-1175
Cervices, carcinoma in situ of both, of didelphic uterus (Wall), 803
Cervix, atresia, congenital, surgical correction (Rotter), 643
carcinoma (*see* Carcinoma of cervix)
excision biopsy (Uhma), 465 (Correspondence)
Cesarean section, antidiuretic activity following (Zuspan, Barnes, and Dillhoefer), 622
followed by radical hysterectomy and pelvic node excision, case (Brunschwig and Barber), 199
rupture of uterus following (Ferguson and Reid), 172; (Pedowitz and Perell), 164
scar, rupture (Ware, Jarrett, and Reda), 184
vaginal delivery after (Ware, Jarrett, and Reda), 186
following, analysis (Riva and Breen), 192
Charlotte of Wales, Princess, confinement (Weekes and Hobbs), 1314
Child, female, urethral obstruction in (Brack and Guild), 1105
Childbirth, all deaths associated with, and maternal mortality rates (Gordon), 204
natural (Rust), 1158 (B. rev.)
painless, psychoprophylactic preparation (Bonstein), 686 (B. rev.)
Chlorothiazide, diuretic action (Matheson and Morgan), 1370 (Abst.)
for edema in pregnancy (Chesley and Ulchanco), 467
oral diuretic (Bayless et al.), 222 (Abst.)
clinical and laboratory studies (Watson, Thompson, and Buchanan), 1371 (Abst.)
Cholelithiasis as complication of pregnancy (Abitbol), 600
Cholesterol, serum, in pregnancy (Wetstone et al.), 481
Cholinesterase activity, studies (Wetstone et al.), 480
Choriocarcinoma, regression of pulmonary metastases after hysterectomy (Garber and Morrison), 812
Chorionepithelioma, 883-896
pulmonary, after term pregnancy (Acosta-Sison), 894
Circulation, digital, in hypertensive pregnant women (Mendlowitz, Altchek, and Naftchi), 473
peripheral, variations during pregnancy (Herbert, Banner, and Wakim), 742
uterine, clearance of radioactive sodium from (Weis, Bruns, and Taylor), 340
Circumcision and carcinoma of cervix (Jones, Macdonald, and Breslow), 4
role in carcinoma of cervix (Heins, Dennis, and Pratt-Thomas), 726
Clinical problems, 675, 1357
Coarctation of aorta, pregnancy and (Goodwin), 220 (Abst.)
in pregnancy (Winter et al.), 582
Colon, rectosigmoid, endometriosis of (Culver, Pereira, and Seibel), 1176
Colpomicroscopy, atlas (Antoine and Grunberger), 688 (B. rev.)
in examination of cervix (Wolfe), 1163
Colporrhagia, postmenopausal, estrogenic ovarian tumors and thecomatosis in (Fienberg), 851
Colporrhaphy, full-thickness anterior, for stress incontinence (Frankel), 1185
Colprosterone, progestational activity (Greenblatt), 626
Columbus, Ohio, cancer survey program (Ullery and Hollenbeck), 1083
Competition and coöperation (Taylor), 931
Constitutional stigmas associated with endometrial carcinoma (Garnet), 11
Contraction, uterine, hemodynamics (Hendricks), 969
Cord, baby, placenta and, relationship (Montgomery), 710
Cornual resection, rupture of uterus due to placenta accreta at site (Hogans and Friedman), 188
Corona radiata cells, role in growth and maturation of ovum (Shettles), 398
Corpus luteum of pregnancy, histology (Nelson and Greene), 67
uteri, carcinoma, radical operation for (Schwartz and Brunschwig), 225 (Abst.)
Correspondence, 227, 464, 1372
Cortisone treatment of congenital adrenal hyperplasia, pregnancy following (Wilson and Keating), 388
Cortisone-induced prolapse and inversion of uterus in mice (Fainstat), 53
Cramp, leg, syndrome during pregnancy (Abrams and Aponte), 432
Culdoscopy, knee rest apparatus for (Riva and Staples), 63
Culture, tissue, endometrial cells in, behavior (Papanicolaou and Maddi), 601
Cultured cancer cells, response to irradiation (Miller et al.), 1071
Curettage, uterine polyp forceps and (Javert), 61

Cysts, ovarian, oxygen tension (Sjöstedt, Rooth, and Caligara), 1228
Cytological aspects of living human ovum (Shettles), 398
diagnosis in gynecological practice (McLaren, Taylor, and Attwood), 925 (Abst.)
screening for cervix cancer (Ullery and Hollenbeck), 1083
Cytology in diagnosis of carcinoma in situ of cervix (Krieger and McCormack), 312
of endometrium (Papanicolaou and Maddi), 601
registry, positive, effect of pregnancy observed from (Ferguson and Cavanagh), 773
urinary, aid in diagnosis (Solomon, Panagotopoulos, and Oppenheim), 56
Cytosmears (Counseller and de Alvarez), 675 (Clinical problems)

D

Dead fetus, prolonged retention (Wheatley), 1283
Death, maternal, heart disease leading cause (Winter et al.), 572
rupture of common bile duct as cause (Abitbol), 599
Decidua, uterine, in ectopic pregnancy (Speert), 491
Deladumone for inhibition of lactation (Stein), 103
Delalutin, progestational activity (Greenblatt), 626
in threatened abortion (Hodgkinson, Igna, and Bukeavich), 279
Delivery of breech, Bracht method (Bellew and Allison), 754
of diabetic patients, optimum time for (Pedowitz and Shlevin), 422
obstetrical, routine hypnosis for (Winkelstein), 152
position for (Montgomery), 708
relationship of baby, placenta, and cord after (Montgomery), 710
vaginal, after cesarean section (Ware, Jarrett, and Reda), 186
analysis (Riva and Breen), 192
Department of current opinion, 210, 443, 675, 917, 1148, 1357
Dextran, radioactive iron-, in pregnancy, absorption (Evans and Ramsey), 925 (Abst.)
Diabetes mellitus and endometrial carcinoma (Garnet), 11
in men, influence on reproduction (Rubin), 1
and pregnancy (Pedowitz and Shlevin), 417
pregnancy with, complicated by hydramnios and loss of fetal movement (Jones), 817
and pregnancy (Gillespie and Ferguson), 679 (Clinical problems)
Diabetic woman, pregnancy in (Reis, DeCosta, and Gerbie), 1148 (Re-evaluation)
Diagnostic pelvic phlebography (Topolanski-Sierra), 44
procedures, gonad radiation dose from (Ardran and Crooks), 456 (Abst.)
Didelphic uterus with carcinoma in situ of both cervices (Wall), 803
Digital vasoconstriction in pregnancy (Mendlowitz, Aitchek, and Naftchi), 473
Diuretic action of chlorothiazide (Matheson and Morgan), 1370 (Abst.)
oral chlorothiazide (Bayless et al.), 222 (Abst.)
clinical and laboratory studies (Watson, Thompson, and Buchanan), 1371 (Abst.)
substance in management of mild preeclampsia (Patterson and Baer), 1264
Diuretics in pregnant women, evaluation (Chesley and Uichanco), 467
Diuril, adjunct to salt-poor diet (Gillespie), 680 (Clinical problems)
in treatment of edema in pregnancy (Chesley and Uichanco), 467
Doriden, use in labor patient (Graves), 1324
Drugs, nature, action, and use (Beckman), 455 (B. rev.)
Ductus arteriosus, murmur from, in newborn (Burnard), 690 (Abst.)
Dysmenorrhea, symptom of adenomyosis (Benson and Sneeden), 1054
teen-age, therapeutic exercises for (Golub et al.), 670
Dysplasia, polyostotic fibrous, and pregnancy (Breen and Riva), 909
Dystocia caused by Wilms's tumor (Copeland, Welburn, and West), 1329
lateral x-ray in (Roberts et al.), 1306
and occipitoposterior (Weekes and Hobbs), 1314

E

Eclampsia, antidiuretic activity in (Zuspan, Barnes, and Dillhoefer), 624
pre-eclamptic toxemia and, etiology (Browne), 221 (Abst.)
pregnancy with thrombocytopenic purpura and (Salzberger and Koren), 1275
Ectopic pregnancy (*see* Pregnancy, ectopic)
Edema, leg, complication of pelvic lymphadenectomy (Gray, Gusberg, and Guttmann), 631
in pregnancy, chlorothiazide for (Chesley and Uichanco), 467
Education, medical (Hunt), 235
Educational Council for Foreign Medical Graduates (E.C.F.M.G.), 213 (Pertinent comments)
Electrolyte balance studies with antihormones (Barnes and Buckingham), 955
concentration of mucus secretion (Abou-Shabanah et al.), 1249
patterns of maternal and fetal blood (Kaiser and Goodlin), 924 (Abst.)
Electron microscope, observations of cervical epithelia with (Dougherty and Low), 839
Electronics, medical, bibliography, 921 (B. rev.)
Embryos, early human, study of (Hertig), 255
Endocrine aspects of breast cancer (Currie), 688 (B. rev.)
basis of Stein-Leventhal syndrome (Leventhal), 830
disorders, hermaphroditism, genital anomalies, and (Jones and Scott), 921 (B. rev.)
function in burns and labor (Mulla), 1338
homotransplants in Millipore filter chambers (Sturgis and Castellanos), 1145
pathology of ovary (Morris and Scully), 1365 (B. rev.)
Endocrines, articles on, 619-628
in gynecology, 53-60
Endocrinological disorders, urinary sediment in study (Solomon, Panagotopoulos, and Oppenheim), 56
Endocrinology, modern trends (Gardiner-Hill), 1364 (B. rev.)
Endometrial cells in tissue culture, behavior (Papanicolaou and Maddi), 601
changes in ectopic pregnancy (Speert), 491
mitosis, indicator of estrogenic activity (Fienberg), 851
Endometriosis, experimental, in human (Ridley and Edwards), 783
pelvic, implantation site of peritoneal pregnancy (Cavanagh), 527
and pseudopregnancy, priority of ideas on (Beecham), 228 (Correspondence)
reply (Kistner), 228 (Correspondence)
rectosigmoid, radiographic features (Culver, Pereira, and Seibel), 1176
Endometrium, adenocarcinoma of (Johnson and Haynes), 335
carcinoma (*see* Carcinoma of endometrium)
cytology (Papanicolaou and Maddi), 601
Enovid, progestational activity (Greenblatt), 627
Epidemiologic factors in carcinoma of cervix (Jones, Macdonald, and Breslow), 1

Epithelia, cervical, fine structure of basement membrane (Dougherty and Low), 839
Epithelium, cervical, colpomicroscopic examination (Wolfe), 1163
Ergonovine in management of placental stage (Fugo and Dieckmann), 141
Erythrocytes with sickle trait, placental transfer (Macris, Hellman, and Watson), 1214
Estinyl in missed abortion (Eastman), 1362 (Clinical problems)
Estradiol valerate and testosterone enanthate (Deladumone) for inhibition of lactation (Stein), 108
Estriol, urinary excretion, and histologic appearance of placenta (Lenters), 1365 (B. rev.)
Estrogen antagonist, effects on electrolyte balance (Barnes and Buckingham), 960
excretion in postmenopausal women (McBride), 691 (Abst.)
and pregnancy, normal (Taylor et al.), 984
Estrogenic thecomatosis, diffuse, in postmenopausal colporrhagia (Fienberg), 851
tumors, ovarian, in postmenopausal colporrhagia (Fienberg), 851
Estrogens, excretion, and carcinoma of cervix (Jones, Macdonald, and Breslow), 9
metabolism, in pregnancy (Davis and Plotz), 939
in missed abortion (Eastman), 1362 (Clinical problems)
precursors (Davis and Plotz), 950
Ethisterone, progestational activity (Greenblatt), 627
Excretion of progesterone metabolites (Davis and Plotz), 940
Exercise, influence on aldosterone secretion (Muller, Manning, and Riondel), 1370 (Abst.)
Exercises, therapeutic, for teen-age dysmenorrhea (Golub et al.), 670
Explants, endometrial, study (Papanicolaou and Maddi), 602
Extrauterine pregnancy, difficulties in diagnosis (Spielman), 462 (Abst.)

F

Fallopian tube, pseudotubercular granulations of (Mautone and Febles Alfonzo), 37
Schistosoma haematobium infection, ectopic pregnancy caused by (El-Bedri), 515
torsion following tubal ligation (Sandler), 41
tubes, role in sterility (Woltz et al.), 736
Fatigue, relationship to prognosis in poliomyelitis in pregnancy (Sharp), 301
Federation of Gynecology and Obstetrics in the French Language, eighteenth congress, 466 (Item)
Feeding at night in infancy, duration (Campbell), 927 (Abst.)
Fertility, 25-36
of diabetic men (Rubin), 27
Fertilization of human ovum (Shettles), 400
Fetal distress in labor, signs (Hellman et al.), 1003
in prolonged pregnancy (Walker), 1235
heart rate, variations (Hellman et al.), 998
loss in pregnancy toxemia (FitzGerald and Clift), 223 (Abst.)
mortality at Sloane Hospital for Women (Steer), 563
salvage with hypothermic-hypotensive technique in toxemia (Barter, Albert, and Winshel), 1067
improved, in diabetes mellitus (Pedowitz and Shlevin), 417
wastage (Steer), 563
weight estimation (McSweeney), 1279
well-being, studies in (Hellman et al.), 998
Fetus, dead, prolonged retention (Wheatley), 1283
effect of ammonium chloride induced maternal acidosis on (Kaiser and Goodlin), 924 (Abst.)
various aspects, 1283-1290
Fistula, vesicovaginal, looped ureteral catheter in repair (Goodwin and Thelen), 641
Follicular and tubal fluids in reproductive process (Balin), 30
Forceps, routine (Montgomery), 709
uterine polyp, and curettage (Javert), 61
Foreign bodies in pelvis after attempted abortion (Friedman and Hogans), 561
Fothergill operation for uterovaginal prolapse (Conger and Keettel), 634
Fundus, uterine, adenocarcinoma of (Johnson and Haynes), 335

G

Galactosemia, congenital, laboratory diagnosis at birth (Schwarz, Holzel, and Komrower), 220 (Abst.)
Gallstones as complication of pregnancy (Abitbol), 600
Gamma globulin, neutralizing antibody for rubella in (Crewman and Ward), 1371 (Abst.)
Ganglion-blocking drugs in hypertensive disease in pregnancy (Dieckmann and Harrod), 379
Gastrocnemius spasm (Secor), 1372 (Correspondence)
Genetic hazards of low-dosage irradiation of ovaries (Israel), 444 (Re-evaluation)
sex, diagnosis by leukocyte morphology, discrepancies (Ashley and Jones), 223 (Abst.)
Genital anomalies and related endocrine disorders, hermaphroditism and (Jones and Scott), 921 (B. rev.)
Geographic distribution of megaloblastic anemia of pregnancy (Agüero and Layrisse), 906
Gestation, masculinization of female fetus by progestins during (Wilkins et al.), 1161 (Abst.)
Glucose tolerance, abnormal, as indication of prediabetic state (Sotto, Heimback, and Siegner), 425
in pregnancy, 17-hydroxycorticosteroids in patients with (Little, Vance, and Rossi), 928 (Abst.)
curves in patients with endometrial carcinoma (Garnet), 17
Glucuronide conjugating system, neonatal development (Brown and Zuelzer), 692 (Abst.)
Glutethimide, use in labor (Graves), 1324
Gonads, radiation dose from diagnostic procedures (Ardran and Crooks), 456 (Abst.)
in obstetric radiography during late pregnancy (Clayton, Farmer, and Warrick), 456 (Abst.)
Gout, pregnancy and (Friedman and Little), 913
and toxemia, clinical antagonism (Friedman and Little), 915
Graft, intestinal seromuscular, reversed, reconstruction of vagina with (Shoemaker et al.), 1194
Grantly Dick Read, challenge of thesis (Rutherford), 929 (Abst.)
Granulosa- and hilus-cell tumors in same ovary (Dougherty, Thompson, and McCall), 653
Gynecologic(al) pathology, study of (Hertig), 269
patient, urinary excretion of antidiuretic substances by (Zuspan, Barnes, and Dillhoefer), 619
practice, cytological diagnosis in (McLaren, Taylor, and Attwood), 925 (Abst.)
recent trends in hysterectomy in (Douglas, Buchman, and MacDonald), 459 (Abst.)

Gynecologic(al)—Cont'd
research in community hospital (Denham and Foraker), 800
Gynecology, articles on, 1-65, 601-674, 825-882, 1163-1208
essentials (Taylor), 1364 (B. rev.)
Manchester-Fothergill operation in (Conger and Keettel), 634
pediatric (Schauffler), 686 (B. rev.)
principles (Jeffcoate), 455 (B. rev.)
textbook of (Brewer), 454 (B. rev.)
urologic injuries in (Falk), 921 (B. rev.)

H

Hapten, Rh, orally administered, effects (Carter and Lewis), 1285
Healing, primary, after irradiation in carcinoma of cervix (Kottmeier), 244
of wounds (Williamson), 686 (B. rev.)
Heart disease complicating pregnancy (Bose), 692 (Abst.)
leading cause of maternal death (Winter et al.), 572
in pregnancy (Masani), 693 (Abst.)
rheumatic, hazard in epidemic of Asian influenza (Greenberg et al.), 901
rate, fetal, variations (Hellman et al.), 998
during uterine contraction (Hendricks), 976
Hematocrit in pregnancy, relationship to cholinesterase activity (Wetstone et al.), 486
Hematoma of rectus abdominis simulating rupture of pregnant uterus (Lucas and Baker), 1302
of umbilical cord (Breen, Riva, and Hatch), 1288
Hemodynamics of uterine contraction (Hendricks), 969
Hemoglobin mass in pregnancy (Lund and Sisson), 1016
Hemorrhage, cause of maternal death (Klein, Clahr, and Tamis), 1344
Hemorrhagic diathesis due to capillary fragility from ovarian deficiency (Wells), 927 (Abst).
Hermaphroditism, genital anomalies, and related endocrine disorders (Jones and Scott), 921 (B. rev.)
Hilus- and granulosa-cell tumors in same ovary (Dougherty, Thompson and McCall), 653
Histochemical studies of 13 day human ovum (Hertig et al.), 1025
Histologic(al) appearance of decidua (Speert), 492, 497-510
of placenta, correlation with estriol excretion (Lenters), 1365 (B. rev.)
observations with the colpomicroscope (Wolfe), 1167
Histology of ovary during pregnancy (Nelson and Greene), 66
Hofbauer, biological barrier (Brown and Hanisch), 719
Homografts, ovarian, in primate (Sturgis and Castellanos), 1132
Hormone assay, clinical application (Loraine), 1364 (B. rev.)
Hormones in blood (Wolstenholme and Millar), 455 (B. rev.)
in human reproduction (Davis and Plotz), 939
steroid, control over electrolyte balance, (Barnes and Buckingham), 955
Hospital, community, gynecologic research in (Denham and Foraker), 800
infection, protection of mother and baby from (Montgomery), 712
Hydatid degeneration of placenta (Kirschbaum), 466 (Correspondence)
Hydatidiform mole, morphology (Hertig), 257
66 cases (Schelpert), 883
Hydramnios, pregnancy with diabetes mellitus complicated by (Jones), 817
Hydrosalpinx in reproductive process (Balin), 30
17-Hydroxycorticosteroids in patient with abnormal glucose tolerance in pregnancy (Little, Vance, and Rossi), 928 (Abst.)
Hypertensive disease in pregnancy, hypotensive drug therapy in (Dieckmann and Harrod), 374
pregnant women, digital vasoconstriction in (Mendlowitz, Altchek, and Naftchi), 473
Hyperthyroidism in patient with postpartum necrosis of pituitary (Fajans), 1160 (Abst.)
Hypnosis for obstetrical delivery (Winkelstein), 152
Hypnosuggestion for obstetrical delivery, evaluation (Winkelstein), 152
Hypofibrinogenemia, abruptio placentae and (Pritchard), 347
acquired, in newborn (Boyd), 929 (Abst.)
Hypophysectomy during pregnancy in patient with breast cancer (Little et al.), 1161 (Abst.)
Hypotensive drug therapy in chronic hypertensive disease in pregnancy (Dieckmann and Harrod), 374
Hypotensive-hypothermic technique in toxemia of pregnancy (Barter, Albert, and Winshel), 1062
Hypothermia, complications (Barter, Albert, and Winshel), 1066
in surgical patient (Barter, Albert, and Winshel), 1065
Hysterectomy, abdominal, rupture of apex of vagina after (Weisse, Watson, and Steffan), 1207
for carcinoma in situ of cervix, carcinoma in situ of vagina after (May), 807
for choriocarcinoma, regression of pulmonary metastases after (Garber and Morrison), 812
and pelvic lymphadenectomy, cervix carcinoma treated by (Carter et al.), 1094
radical, after cesarean section, case (Brunschwig and Barber), 199
recent trends, in gynecological and obstetrical practice (Douglas, Buchman, and MacDonald), 459 (Abst.)
role in treatment of carcinoma in situ of cervix (Krieger and McCormack), 316
Hysterosalpingography, complications (Woltz et al.), 736

I

Implantation site, histochemical features (Hertig et al.), 1030
Impotence, incidence in diabetic men (Rubin), 25
Incontinence, stress, urethrovesicopubic relationships and (Hodgkinson and Kelly), 1114
vaginal plastic operation for (Frankel), 1185
Induction of labor (*see* Labor, induction)
Infection, biological barrier of Hofbauer (Brown and Hanisch), 719
cause of maternal death (Klein, Clahr, and Tamis), 1345
hospital, protection of mother and baby from (Montgomery), 712
intrauterine, and perinatal mortality (Flowers et al.), 765
Infertility, diagnosis, etiology, and prognosis (Johanssen), 923 (Abst.)
Stein-Leventhal syndrome associated with (Leventhal), 827
Influenza, Asian, epidemic, maternal mortality in New York City, 1957 (Greenberg et al.), 897
Interlocking of twins, chin-to-chin (Kreis and Miller), 1334
Internal medicine as medical specialty (Taylor), 934
Intestinal grafts, reconstruction of vagina with (Shoemaker et al.), 1194
Intrauterine bougie and Voorhees bag, present status (Taylor), 553

Inversion, postpartum, of unicornuate uterus (McDuff and Keegan), 1299
of uterus, cortisone induced (Fainstat), 53
Ireland, ABO and simple Rh blood groupings in (Hackett and Dawson), 691 (Abst.)
Iron and calcium administration, effects, in pregnancy and newborn (Lapan and Friedman), 96
Iron-dextran, radioactive, in pregnancy, absorption (Evans and Ramsey), 925 (Abst.)
Irradiation (*see also* Radiation)
of carcinoma of cervix at Radiumhemmet (Kottmeier), 250
technique (Kottmeier), 247
and early surgery for endometrial carcinoma (Decker), 20
low-dosage, of ovaries, repudiation (Israel), 443 (Re-evaluation)
sensitivity of cervix cancer (Miller et al.), 1071
supervoltage, for squamous-cell carcinoma of cervix (Rutledge and Fletcher), 321
technique with 22 Mev betatron (Rutledge and Fletcher), 325
treatment of carcinoma of cervix (Kottmeier), 243
x-ray, directed to pituitary and ovaries for sterility (Kaplan), 447 (Re-evaluation)
Items, 226, 466, 930, 1162

J

Japanese woman with Caucasian husband, obstetric risk (Sargent, Westfall, and Adams), 137

K

Knee rest apparatus for culdoscopy patient (Riva and Staples), 63
Kraurosis-leukoplakia syndrome, topical testosterone in (Richardson and Williams), 791

L

Labor, abnormal (Calkins), 218 (B. rev.)
analgesia and anesthesia in (Montgomery), 707
duration, and perinatal mortality (Flowers et al.), 765
dystocic, lateral x-ray in (Roberts et al.), 1306
fetal distress in (Hellman et al.), 1003
induction (Montgomery), 707
with bougie (Taylor), 554
death from, and death from postmaturity, choice (Gibberd), 1369 (Abst.)
with intra-amniotic injection of Prostigmin methylsulfate (Fernandes, Junior, and Fernandez), 1367 (Abst.)
in prolonged pregnancy (Walker), 1238
relaxin for (Stone, Sedlis, and Zuckerman), 548
with Voorhees bag (Taylor), 555
management, 141-160, 544-557, 1306-1341
outcome, x-ray pelvimetry and (Steer), 118
premature, and delayed disappearance of radioactive sodium from myometrium (Weis, Bruns, and Taylor), 340
treatment with relaxin (Stone, Sedlis, and Zuckerman), 546
in prolonged pregnancy (Walker), 1236, 1238
and puerperium, physiologic considerations (Montgomery), 706
after severe thermal burns (Mulla), 1338
theory, contractions of uterus and (Goldfarb), 224 (Abst.)
uterine, rupture in (Bancroft-Livingston and Myles), 690 (Abst.)
in young primigravida (Poliakoff), 749
Lactating women, effect of intranasal oxytocin on let-down of milk in (Newton and Egli), 103
oxytocin in (Hawker), 1160 (Abst.)
Lactation, inhibition, evaluation of Deladumone for (Stein), 108
Leg cramp syndrome (Secor), 1372 (Correspondence)
during pregnancy (Abrams and Aponte), 432
Legacy, every man's (Hunt), 235
Legal abortion in Sweden (Arén), 689 (Abst.)
Leprosy, pregnancy and (King and Marks), 438
Let-down reflex, effect of intranasal oxytocin (Newton and Egli), 103
Leukocyte morphology, diagnosis of genetic sex by, discrepancies (Ashley and Jones), 223 (Abst.)
Leukoplakia, kraurosis and, topical testosterone in (Richardson and Williams), 791
Levarterenol bitartrate therapy in operative shock (Dew), 1201
Levophed therapy in operative shock (Dew), 1201
Liver function in pregnancy (Wetstone et al.), 480
Lupus erythematosus factor, placental transmission (Mijer and Olsen), 918 (Abst.)
Lutocylol, progestational activity (Greenblatt), 626
Lymph node involvement in carcinoma of cervix, incidence (Rutledge and Fletcher), 321
pelvic, dissection, after radiotherapy (Gray, Gusberg, and Guttmann), 629
Lymphadenectomy, pelvic, and hysterectomy, cervix carcinoma treated by (Carter et al.), 1094
lymphocysts, complication of (Gray, Gusberg, and Guttmann), 632
transperitoneal pelvic, following supervoltage irradiation for squamous-cell carcinoma of cervix (Rutledge and Fletcher), 321
Lymphocysts, complication of pelvic lymphadenectomy (Gray, Gusberg, and Guttmann), 632
Lymphoma, malignant, involving ovaries (Nelson et al.), 861

M

Male nuclear sex with ovarian tissue (Ashley and Jones), 1369 (Abst.)
reproductive capacity, influence of diabetes mellitus on (Rubin), 25
Malformation, congenital, following rubella (Crewman and Ward), 1371 (Abst.)
following irradiation for sterility (Kaplan), 449 (Re-evaluation)
Malignancy, problem, after Manchester operation (Conger and Keettel), 639
Malignant endometrial neoplasms, tissue culture study (Papanicolaou and Maddi), 602
endometrium, tissue culture, 612-616
lymphoma involving ovaries (Nelson et al.), 861
Manchester-Fothergill operation for uterovaginal prolapse (Conger and Keettel), 634
Maneuver, Bracht, description (Bellew and Allison), 754
Marital status, role in pre-eclampsia (Salerno), 1272
Masculinization of female fetus by progestins during gestation (Wilkins et al.), 1161 (Abst.)
Masculinizing tumors of ovary (Dougherty, Thompson, and McCall), 653
Mastectomy, radical, in cancer of breast, results at Mayo Clinic (Berkson et al.), 462 (Abst.)
Mastitis, puerperal, treatment with x-ray (Grasberger and Zeiss), 226 (Abst.)

Maternal blood volume and anemia (Lund and Sisson), 1013
death, heart disease leading cause (Winter et al.), 572
rupture of common bile duct as cause (Abitbol), 599
deaths in Bronx County, New York, 1946-1957 (Klein, Clahr, and Tamis), 1342
mortality in epidemic of Asian influenza, New York City, 1957 (Greenberg et al.), 897
rates and all deaths associated with childbirth, relation (Gordon), 204
Maternal-fetal barrier, A-B-O(H) blood group substances in (Freda), 407
Meconium, sign of fetal distress (Hellman et al.), 1005
Medical education (Hunt), 235
electronics, bibliography on, 921 (B. rev.)
practice, psychology, 1156 (B. rev.)
Megaloblastic anemia of pregnancy in Venezuela (Agüero and Layrisse), 903
Membrane, basement, of cervical epithelia, fine structure (Dougherty and Low), 839
Membranes, fetal, congenital defect simulating spontaneous rupture (Reisfield), 458 (Abst.)
spontaneous premature rupture (Flowers et al.), 761
Memphis plan of cancer survey (Ullery and Hollenbeck), 1084
Menopause, Manchester operation before (Conger and Keettel), 640
Menorrhagia, symptom of adenomyosis (Benson and Sneeden), 1054
Menstrual cycle, growth of endometrial explants during (Papanicolaou and Maddi), 603
Metabolism of C^{14}-progesterone in human subjects (Sandberg and Slaunwhite), 1160 (Abst.)
of N^{15}-labeled uric acid in pregnant women (Seitchik, Szutka, and Alper), 1151 (Re-evaluation)
steroid, in human pregnancy (Davis and Plotz), 939
Metabolites of progesterone, two naturally occurring (Zander et al.), 1160 (Abst.)
Metastases, pulmonary, regression after hysterectomy for choriocarcinoma (Garber and Morrison), 812
Microscope, electron, observations of cervical epithelia with (Dougherty and Low), 839
Millipore filter chambers, ovarian transplants in (Sturgis and Castellanos), 1132
Mitosis, endometrial, indicator of estrogenic activity (Fienberg), 851
Mitral stenosis, rheumatic, in pregnancy (Winter et al.), 580
Mole, hydatidiform (Schelpert), 883
Morphologic anomalies of the placenta (Agüero), 454 (B. rev.)
Mortality, fetal, at Sloane Hospital for Women (Steer), 563
maternal, in Bronx County, New York, 1946-1957 (Klein, Clahr, and Tamis), 1342
in epidemic of Asian influenza, New York City, 1957 (Greenberg et al.), 897
perinatal, dynamic investigation (Williams et al.), 305
influence of social factors on (Käser), 463 (Abst.)
in prolonged pregnancy (Walker), 1233
rates (Steer), 565
role of premature rupture of membranes in (Flowers et al.), 764
statistics (Gold, Jacobziner, and Pakter), 229 (Correspondence)
reply (Hess), 229 (Correspondence)
Mortality—Cont'd
rates, maternal, and all deaths associated with childbirth, relation (Gordon), 204
and survival in surgically treated cancer of breast (Berkson et al.), 462 (Abst.)
Mosher exercises for dysmenorrhea (Golub et al.), 670
Mother and baby, protection from hospital infection (Montgomery), 712
relationship after delivery (Montgomery), 711
Mucus smear, nasal, in toxemias of pregnancy (Abou-Shabanah), 1248
Murmur from ductus arteriosus in newborn (Burnard), 690 (Abst.)
Myomectomy, rupture of uterus following (Pedowitz and Perell), 164
Myometrium, disappearance of radioactive sodium from, in pregnancy (Weis, Bruns, and Taylor), 340
sodium clearance from (Taylor et al.), 987

N

Nail, removal from parametrium (Friedman and Hogans), 561
Nasal mucus smear in toxemias of pregnancy (Abou-Shabanah et al.), 1248
Natural childbirth (Rust), 1158 (B. rev.)
Neonatal development of glucuronide conjugating system (Brown and Zuelzer), 692 (Abst.)
Neoplasm, ovarian, levarterenol bitartrate therapy following removal (Dew), 1201
Neurectomy, presacral, neurofibroma following (Goldenberg and Alderman), 1204
Neurofibroma after presacral neurectomy (Goldenberg and Alderman), 1204
Neurogenic vasoconstriction, in digital circulation (Mendlowitz, Altchek, and Naftchi), 478
Neurological factors in pre-eclampsia-eclampsia (Salerno), 1269
Newborn (infant) acquired hypofibrinogenemia in (Boyd), 929 (Abst.)
with anoxia, behavior test performance (Graham et al.), 461 (Abst.)
blood studies in (Lapan and Friedman), 96
hematologic state (Lund and Sisson), 1018
murmur from ductus arteriosus in (Burnard), 690 (Abst.)
staphylococcal peritonitis in (Beaven), 926 (Abst.)
venous pressure in (Parkinson), 461 (Abst.)
Nilevar, progestational activity (Greenblatt), 627
Nipple, development in pregnancy (Hytten and Baird), 137 (Abst.)
Node excision, pelvic, and radical hysterectomy after cesarean section (Brunschwig and Barber), 199
panhysterectomy and, for carcinoma of corpus uteri (Schwartz and Brunschwig), 225 (Abst.)
lymph, pelvic, dissection after radiotherapy (Gray, Gusberg, and Guttmann), 629
l-Norepinephrine in shock therapy (Dew), 1202
Norlutin, progestational activity (Greenblatt), 627
in threatened abortion (Hodgkinson, Igna, and Bukeavich), 279
19-Nortestosterone derivatives, progestational activity (Greenblatt), 627
Nuclear sex, male, with ovarian tissue (Ashley and Jones), 1369 (Abst.)
Nurses' time, conservation (Taylor), 215 (Pertinent comments)

Nutritional factors in carcinoma of cervix (Jones, Macdonald, and Breslow), 4

O

Obstetric(al) analgesia and sedation, promethazine as adjunct (Gordon and Ruffin), 147
causes of death, Bronx County, New York, 1946-1957 (Klein, Clahr, and Tamis), 1343
pathology, career in (Hertig), 254
patient, urinary excretion of antidiuretic substances by (Zuspan, Barnes, and Dillhoefer), 619
patients, self-medication and control of visiting (Taylor), 215 (Pertinent comments)
practice, private, acute poliomyelitis in (Sharp), 299
recent trends in hysterectomy in (Douglas, Buchman, and MacDonald), 459 (Abst.)
radiographic examinations, maternal and fetal radiation dosage during (Bewley, Laws, and Myddleton), 456 (Abst.)
radiography in late pregnancy, radiation doses to gonads in (Clayton, Farmer, and Warrick), 456 (Abst.)
risk of Japanese woman with Caucasian husband (Sargent, Westfall, and Adams), 137
Obstetrics, articles on, 66-209, 398-442, 467-600, 883-916, 1209-1356
hypothermia in (Barter, Albert, and Winshel), 1065
modern practice (Stern and Burnett), 1365 (B. rev.)
text (Merger, Lévy, and Melchior), 219 (B. rev.)
Obstruction, urethral, in female child (Brack and Guild), 1105
Occipitoposterior position and dystocia (Weekes and Hobbs), 1314
Omental transference, theory of peritoneal pregnancy (Cavanagh), 529
Orally administered Rh hapten (Carter and Lewis), 1285
Orinase screening test in diabetes (Gillespie), 679 (Clinical problems)
Ovarian cysts, oxygen tension (Sjöstedt, Rooth, and Caligara), 1228
deficiency, hemorrhagic diathesis due to capillary fragility from (Wells), 927 (Abst.)
estrogenic tumors in postmenopausal colporrhagia (Fienberg), 851
hemografts in primate (Sturgis and Castellanos), 1132
neoplasm, levarterenol bitartrate therapy after removal (Dew), 1201
pregnancy, primary (Moyers and Lack), 518
tissue with male nuclear sex (Ashley and Jones), 1369 (Abst.)
tumors, 647-657, 851-882
Ovaries, bilateral polycystic (Leventhal), 825
low-dosage irradiation of, repudiation (Israel), 443 (Re-evaluation)
malignant lymphoma involving (Nelson et al.), 861
x-ray treatment of female sterility directed to (Kaplan), 447 (Re-evaluation)
Ovary, carcinoma, statistical validity of figures on therapy (Caldwell and Latour), 464 (Correspondence)
endocrine pathology (Morris and Scully), 1365 (B. rev.)
hilus- and granulosa-cell tumors in same (Dougherty, Thompson, and McCall), 653
histology during pregnancy (Nelson and Greene), 66
malignant Brenner tumor of (Reel), 872
in Stein-Leventhal syndrome (Leventhal), 832
Ovum, living human (Shettles), 398
13 day human, studied histochemically (Hertig et al.), 1025
Oximetry, control of supplemental oxygen by (Swyer and Weight), 459 (Abst.)
Oxygen levels in babies from prolonged pregnancies (Walker), 1237
supplemental, control by oximetry (Swyer and Weight), 459 (Abst.)
tension of amniotic fluid (Sjöstedt, Rooth, and Caligara), 1226
Oxytocic drugs in management of placental stage, comparison (Fugo and Dieckmann), 141
Oxytocin, intranasal, effect on let-down of milk (Newton and Egli), 103
in lactating women (Hawker), 1160 (Abst.)
Oxytocin-sensitivity test for uterine irritability (Smyth), 222 (Abst.)

P

Pain, adenomyosis as cause (Benson and Sneeden), 1054
Palsy, cerebral, and twins (Gingras et al.), 1367 (Abst.)
Panhysterectomy, radical, and pelvic node excision for carcinoma of corpus uteri (Schwartz and Brunschwig), 225 (Abst.)
Papanicolaou technique in cancer survey program (Ullery and Hollenbeck), 1084
Parametrium, removal of nail from (Friedman and Hogans), 561
Pathogenicity of *Trichomonas vaginalis* (Burch, Rees, and Kayhoe), 658
Pathology, gynecologic, study of (Hertig), 269
obstetric, career in (Hertig), 254
of ovary, endocrine (Morris and Scully), 1365 (B. rev.)
surgical, of Stein-Leventhal syndrome (Plate), 1368 (Abst.)
Pediatric gynecology (Schauffler), 686 (B. rev.)
practice, allergy in (Thalhammer), 219 (B. rev.)
Pediatrics as medical specialty (Taylor), 935
Pelvic congestion, evaluation by phlebography (Topolanski-Sierra), 57
lymphadenectomy following radiotherapy (Gray, Gusberg, and Guttmann), 629
measurement, 118-140
measurements of Japanese women (Sargent, Westfall, and Adams), 137
node excision, radical hysterectomy and, after cesarean section (Brunschwig and Barber), 199
panhysterectomy and, for carcinoma of corpus uteri (Schwartz and Brunschwig), 225 (Abst.)
phlebography (Topolanski-Sierra), 44
Pelvimetry, intrapartum, in dystocic labors (Roberts et al.), 1306
x-ray, and outcome of labor (Steer), 118
Perforation of uterus by catheter (Speidel and Hatch), 558
Perinatal casualties, institute on, 930 (Item)
loss and fetal distress in labor (Hellman et al.), 1004
mortality, dynamic investigation (Williams et al.), 305
influence of social factors on (Käser), 463 (Abst.)
in prolonged pregnancy (Walker), 1233
rates (Steer), 565
role of premature rupture of membranes in (Flowers et al.), 764
statistics (Gold, Jacobziner, and Pakter), 229 (Correspondence)
reply (Hess), 229 (Correspondence)

Peritoneal cavity, blood in, fate (Pritchard and Adams), 224 (Abst.)
pregnancy, primary (Cavanagh), 523
Peritonitis, staphylococcal, in newborn (Beaven), 926 (Abst.)
Pertinent comments, 210, 917
Phagocytosis in endometrium (Papanicolaou and Maddi), 601, 609
Pharmacology of drugs (Beckman), 455 (B. rev.)
Phenergan hydrochloride in obstetrical analgesia and sedation (Gordon and Ruffin), 148
Phlebography, pelvic (Topolanski-Sierra), 44
Phonocardiograph, fetal heartbeat recorded by (Hellman et al.), 1000
Phosphorus metabolism, leg cramp syndrome and (Abrams and Aponte), 432
Physical aids, 61-65
Physiochemical disturbances in pre-eclampsia-eclampsia (Salerno), 1268
Physiologic considerations in labor and puerperium (Montgomery), 706
Physiology of pregnancy, 91-102 (Wetstone et al.), 480
Pitocin, cardiovascular reactions (Reinberger and Mackey), 288
in management of placental stage (Fugo and Dieckmann), 141
Pitressin and Pitocin, specific effects (Reinberger and Mackey), 288
Pituitary gland, anterior, role in Stein-Leventhal syndrome (Leventhal), 830
low-dosage irradiation of (Israel), 443, 445 (Re-evaluation)
postpartum necrosis, hyperthyroidism in patient with, 1160 (Abst.)
stalk section in goat, effects (Daniel and Prichard), 1366 (Abst.)
x-ray treatment of female sterility directed to (Kaplan), 447 (Re-evaluation)
Pituitrin, use as oxytocic, warning against (Reinberger and Mackey), 289
Placenta accreta at site of cornual resection, rupture of uterus due to (Hogans and Friedman), 188
and amnion, function, 1209-1230
and cord, baby and, relationship (Montgomery), 710
elimination through bladder (Hunter et al.), 539
histologic appearance, estriol excretion correlated with (Lenters), 1365 (B. rev.)
hydatid degeneration (Kirschbaum), 466 (Correspondence)
morphologic anomalies (Agüero), 454 (B. rev.)
premature separation, and hypofibrinogenemia (Pritchard), 347
previa, one radiograph to exclude (Earn, Freer, and Cairns), 926 (Abst.)
toxemia and (Friedman and Little), 919 (Pertinent comments)
coexistence and symptomatology (Shanklin), 227 (Correspondence)
reply (Bieniarz), 227 (Correspondence)
rabbit, permeability to homologous albumin (Winkler, Fitzpatrick, and Finnerty), 1209
size and weight (Taylor et al.), 993
Placental activity, tests for disappearance (Weinberg, Salz, and Funaro), 542
function, measurment (Taylor et al.), 983
stage, oxytocic drugs in management, comparison (Fugo and Dieckmann), 141
tissue, A-B-O(H) blood group substances in (Freda), 407
transfer of transfused sickle-trait cells (Macris, Hellman, and Watson), 1214
transfusion (Lund and Sisson), 1019
Placental—Cont'd
transmission of L.E. factor (Mijer and Olsen), 928 (Abst.)
Poliomyelitis, acute, in private obstetrical practice (Sharp), 299
Polyostotic fibrous dysplasia and pregnancy (Breen and Riva), 909
Position, influence, on aldosterone secretion (Muller, Manning, and Riondel), 1370 (Abst.)
Postmaturity (Wrigley), 928 (Abst.)
clinical (Walker), 1244
death from, and death from induction of labor, choice (Gibberd), 1369 (Abst.)
Postmenopausal colporrhagia, estrogenic ovarian tumors and thecomatosis in (Fienberg), 851
vaginal bleeding, problem (Fienberg), 851
women, estrogen excretion in (McBride), 691 (Abst.)
Postoperative period, antidiuretic activity (Zuspan, Barnes, and Dillhoefer), 622
Postpartum nurses' time, conservation (Taylor), 215 (Pertinent comments)
Pranone, progestational activity (Greenblatt), 626
Précis d'obstétrique (Merger, Lévy, and Melchior), 219 (B. rev.)
Predema in mild pre-eclampsia (Patterson and Baer), 1265
"Prediabetic state," unsuspected, and pregnancy (Sotto, Heimback, and Siegner), 425
Pre-eclampsia, mild, diuretic substance in management (Patterson and Baer), 1264
Pre-eclamptic toxemia and eclampsia, etiology (Browne), 221 (Abst.)
Pregnancy, abdominal, with elimination of placenta through bladder (Hunter et al.), 539
secondary (Cavanagh), 523; (Hunter et al.), 539
term (Weinberg, Salz, and Funaro), 542
with survival (Barber and Rathbun), 822
uterine decidua in (Speert), 508-510
abnormal, 1231
glucose tolerance in, 17-hydroxycorticosteroids in (Little, Vance, and Rossi), 928 (Abst.)
absorption of vitamin B_{12} in, with reference to effect of D-sorbitol (Chow et al.), 91
after adrenogenital syndrome (Erez and Yenen), 877
appendicitis in (Soelling), 1291
blood studies in (Lapan and Friedman), 96
volume and anemia in (Lund and Sisson), 1013
carcinoma of cervix in (Holzaepfel and Ezell), 292
treated by cesarean section and radical operation (Brunschwig and Barber), 199
cardiac disease in (Masani), 693 (Abst.)
diseases complicating (Bose), 692 (Abst.)
surgery in (Winter et al.), 572
cervical, uterine decidua in (Speert), 496, 500-501
chlorothiazide for edema in (Chesley and Uichanco), 467
cholelithiasis as complication (Abitbol), 600
and coarctation of aorta (Goodwin), 220 (Abst.)
complications, 1291-1305
corpus luteum of, histology (Nelson and Greene), 67
diabetes and (Gillespie and Ferguson), 679
mellitus and (Pedowitz and Shlevin), 417
complicated by hydramnios and loss of fetal movements (Jones), 817

Pregnancy—Cont'd
in diabetic woman (Reis, DeCosta, and Gerbie), 1148 (Re-evaluation)
digital vasoconstriction in (Mendlowitz, Altchek, and Naftchi), 473
disappearance of radioactive sodium from uterine muscle in (Weis, Bruns, and Taylor), 340
ectopic, 491-543
caused by *Schistosoma haematobium* infection (El-Bedri), 515
uterine decidua in (Speert), 491
effect, observed from positive cytology registry (Ferguson and Cavanagh), 773
extrauterine, difficulties in diagnosis (Spielman), 462 (Abst.)
and gout (Friedman and Little), 913
hazard in epidemic of Asian influenza (Greenberg et al.), 901
hematocrit in, relationship to cholinesterase activity (Wetstone et al.), 486
heterotopic (Zlatnik et al.), 536
histology of ovary during (Nelson and Greene), 66
hypertensive disease in, hypotensive drug therapy (Dieckmann and Harrod), 374
hypophysectomy during, for breast cancer (Little et al.), 1161 (Abst.)
incidence of poliomyelitis in (Sharp), 299
intrauterine and tubal, combined (Zlatnik et al.), 536
late, uterine rupture in (Bancroft-Livingston and Myles), 690 (Abst.)
leg cramp syndrome during (Abrams and Aponte), 432
and leprosy (King and Marks), 438
liver function in (Wetstone et al.), 480
masculinization of female fetus by progestins during (Wilkins et al.), 1161 (Abst.)
medical complications, 897-916
megaloblastic anemia of, in Venezuela (Agüero and Layrisse), 903
nipple development in (Hytten and Baird), 1371 (Abst.)
ovarian, primary (Moyers and Lack), 518
peritoneal, primary (Cavanagh), 523
physiology, 91-102
(Wetstone et al.), 480
polyostotic fibrous dysplasia and (Breen and Riva), 909
prolonged, syndrome (Walker), 1231
radioactive iron-dextran absorption in (Evans and Ramsey), 925 (Abst.)
radiography during, radiation doses to gonads in (Clayton, Farmer, and Warrick), 456 (Abst.)
rupture of spleen in (Sparkman), 587
salt in (Robinson), 222 (Abst.)
salvage with high potency progesterone drugs in threatened abortion (Hodgkinson, Igna, and Bukeavich), 281
steroid metabolism in (Davis and Plotz), 939
surgical complications, articles on, 572-600
term, pulmonary chorionepithelioma after (Acosta-Sison), 894
test, progesterone-induced withdrawal bleeding as (Hayden), 271
with thrombocytopenic purpura and eclampsia (Salzberger and Koren), 1275
toxemia (*see* Toxemia of pregnancy)
after treatment of congenital adrenal hyperplasia with cortisone (Wilson and Keating), 388
tubal and intrauterine, combined (Zlatnik et al.), 536
twin, unilateral (Demick and Cavanagh), 533
uterine decidua in (Speert), 496-499, 502-507, 510-511
Pregnancy—Cont'd
unsuspected "prediabetic state" and (Sotto, Heimback, and Siegner), 425
variations in peripheral circulation during (Herbert, Banner, and Wakim), 742
in young primigravida (Poliakoff), 746
Pregnanediol excretion, normal, and pregnancy (Taylor et al.), 986
Pregnant uterus, hematoma of rectus abdominis simulating rupture (Lucas and Baker), 1302
women, uric acid metabolism in (Seitchik, Szutka, and Alper), 1151 (Re-evaluation)
Premature infant, care (Lundeen and Kunstadter), 1158 (B. rev.)
labor and delayed disappearance of radioactive sodium from myometrium (Weis, Bruns, and Taylor), 340
Prematurity, leading cause of fetal mortality (Steer), 566
Presacral neurectomy, neurofibroma follow- (Goldenberg and Alderman), 1204
Primigravida, young, pregnancy in (Poliakoff), 746
Primiparity, role in pre-eclampsia (Salerno), 1272
Princess Charlotte of Wales, confinement (Weekes and Hobbs), 1314
Prodox, progestational activity (Greenblatt), 626
Progesterone compounds, clinical test for efficacy (Greenblatt), 626
high potency, and threatened abortion (Hodgkinson, Igna, and Bukeavich), 279
metabolism in pregnancy (Davis and Plotz), 939
radioactive, metabolism (Sandberg and Slaunwhite), 1160 (Abst.)
two naturally occurring metabolites of (Zander), 1160 (Abst.)
Progesterone-induced withdrawal bleeding as test for pregnancy (Hayden), 271
Progestins during gestation, masculinization of female fetus by (Wilkins et al.), 1161 (Abst.)
Prolapse, uterovaginal, Manchester-Fothergill operation for (Conger and Keettel), 634
of uterus, cortisone induced (Fainstat), 53
Promethazine in obstetrical analgesia and sedation (Gordon and Ruffin), 147
Prostigmin methylsulfate, intra-amniotic injection for induction of labor (Fernandes, Junior, and Fernandes), 1367 (Abst.)
Proteins, serum, in pregnancy (Wetstone et al.), 483
Protoveratrine A and B in hypertensive disease in pregnancy (Dieckmann and Harrod), 377
Pseudohermaphrodism, adrenal, with later pregnancy (Erez and Yenen), 877
female, nonadrenal (Wilkins et al.), 1161 (Abst.)
Pseudomonas sepsis and stillbirth, bacteremic shock with (Pennisi, Lawrence, and Veprovsky), 1294
Pseudopregnancy and endometriosis, priority of ideas on (Beecham), 228 (Correpondence)
reply (Kistner), 228 (Correspondence)
Pseudotubercular granulations of Fallopian tube (Mautone and Febles Alfonzo), 37
Psychiatry as medical specialty (Taylor), 936
Psychoendocrinology (Reiss), 1157 (B. rev.)
Psychology of medical practice (Hollender), 1156 (B. rev.)
Psychophysical stress and carcinoma of cervix (Jones, Macdonald, and Breslow), 8

Psychophysiologic aspects of toxemias of pregnancy (Salerno), 1268
Psychoprophylactic preparation for painless childbirth (Bonstein), 686 (B. rev.)
Puerperal mastitis, treatment with x-ray (Grasberger and Zeiss), 226 (Abst.)
states, antidiuretic activity in (Zuspan, Barnes, and Dillhoefer), 623, 624
Puerperium, electrolyte balance in (Barnes and Buckingham), 957
physiologic considerations (Montgomery), 706
Pulmonary chorionepithelioma after term pregnancy (Acosta-Sison), 894
metastases, regression after hysterectomy for choriocarcinoma (Garber and Morrison), 812
Purpura, thrombocytopenic, and eclampsia, pregnancy with (Salzberger and Koren), 1275

R

Radiation (*see also* Irradiation)
dosage, maternal and fetal, during obstetric radiographic examinations (Bewley, Laws, and Myddleton), 456 (Abst.)
dose to gonads from diagnostic procedures (Ardran and Crooks), 456 (Abst.)
doses to fetal and maternal gonads in obstetric radiography in late pregnancy (Clayton, Farmer and Warrick), 456 (Abst.)
ionizing, damage to genes from (Israel), 444 (Re-evaluation)
Radioactive iron-dextran in pregnancy, absorption (Evans and Ramsey), 925 (Abst.)
sodium, disappearance from uterine muscle in pregnancy (Weis, Bruns, and Taylor), 340
Radiograph, single, to exclude placenta previa (Earn, Freer, and Cairns), 926 (Abst.)
Radiographic features of rectosigmoid endometriosis (Culver, Pereira, and Seibel), 1176
Radiography, obstetric, radiation dosage during (Bewley, Laws, and Myddleton), 456 (Abst.)
doses to gonads in (Clayton, Farmer, and Warrick), 456 (Abst.)
Radiosensitivity of carcinoma of cervix (Kottmeier), 246
Radiotherapy as medical speciality (Taylor), 934
pelvic lymphadenectomy following (Gray, Gusberg, and Guttmann), 629
Radiumhemmet, irradiation of carcinoma of cervix at (Kottmeier), 250
Read, Grantly Dick, challenge of thesis (Rutherford), 929 (Abst.)
Rectal bleeding, symptom of rectosigmoid endometriosis (Culver, Pereira, and Seibel), 1177
Rectosigmoid endometriosis, radiographic features (Culver, Pereira, and Seibel), 1176
Rectus abdominis muscle, hematoma of, simulating rupture of pregnant uterus (Lucas and Baker), 1302
Re-evaluation, 443, 1148
Relaxin, critical evaluation (Stone, Sedlis, and Zuckerman), 544
Releasin, effects upon cervix at term (Stone, Sedlis, and Zuckerman), 551
Reproduction, follicular and tubal fluids in (Balin), 30
hormones in (Davis and Plotz), 939
influence of diabetes mellitus in men (Rubin), 25
studies (Rubin), 25
Research program, evolution (Hertig), 252
Resectoscope, use in children with urethral obstruction (Brack and Guild), 1110
Residency review committee in obstetrics and gynecology, 917 (Pertinent comments)
Rh hapten, orally administered, effects (Carter and Lewis), 1285
simple, blood groups in Ireland, distribution (Hackett and Dawson), 691 (Abst.)
Rheumatic heart disease, hazard in epidemic of Asian influenza (Greenberg et al.), 901
mitral stenosis in pregnancy (Winter et al.), 580
Rooming-in of babies with mothers (Montgomery), 712
Roster of American obstetrical and gynecological societies, 230
Rubella, neutralizing antibody in gamma globulin for (Crewman and Ward), 1371 (Abst.)
Rupture of membranes, spontaneous, congenital defect simulating (Reisfield), 458 (Abst.)
premature (Flowers et al.), 761
of pregnant uterus, hematoma of rectus abdominis simulating (Lucas and Baker), 1302
of uterus (Pedowitz and Perell), 161
at Boston Lying-in Hospital (Ferguson and Reid), 172
due to placenta accreta at site of previous cornual resection (Hogans and Friedman), 188
gravid (Ware, Jarrett, and Reda), 181
of vagina after abdominal hysterectomy (Weisse, Watson, and Steffan), 1207

S

Salt in pregnancy (Robinson), 178 (Abst.)
Sampson's theory of endometriosis, evidence for (Ridley and Edwards), 789
Sarcoma botryoides, two cases (Miller), 1172
Sarcoma 37, effects of mixed bacterial toxins on (Donnelly, Havas, and Groesbeck), 460 (Abst.)
Schistosoma haematobium infection, ectopic pregnancy caused by (El-Bedri), 515
Sciences, basic medical, and obstetrics and gynecology (Taylor), 936
Secobarbital sodium, comparison of glutethimide with, in labor (Graves), 1324
Sedation, obstetrical, promethazine as adjunct (Gordon and Ruffin), 147
Sedative action of glutethimide in labor (Graves), 1324
Self-medication of obstetric patients (Taylor), 215 (Pertinent comments)
Sepsis, Pseudomonas, and stillbirth, bacteremic shock with (Pennisi, Lawrence, and Veprovsky), 1294
Seromuscular grafts, reversed, reconstruction of vagina with (Shoemaker et al.), 1194
Serum, fetal and maternal, free amino acids in (Wirtschafter), 1219
Sex, genetic, diagnosis by leukocyte morphology, discrepancies (Ashley and Jones), 223 (Abst.)
nuclear, male, with ovarian tissue (Ashley and Jones, 1369 (Abst.)
Sexual practices and carcinoma of cervix (Jones, Macdonald, and Breslow), 5
Shock, bacteremic, with pseudomonas sepsis and stillbirth (Pennisi, Lawrence, and Veprovsky), 1294
operative, levarterenol bitartrate therapy in (Dew), 1201
Sickle-trait cells, transfused, placental transfer (Macris, Hellman, and Watson), 1214

Smear, nasal mucus, in toxemias of pregnancy (Abou-Shabanah), 1248
Smegma, role in carcinoma of cervix (Heins, Dennis, and Pratt-Thomas), 726
Social factors, influence on perinatal mortality (Käser), 463 (Abst.)
Socioeconomic factors in carcinoma of cervix (Jones, Macdonald, and Breslow), 4
in perinatal mortality (Flowers et al.), 767
Sodium clearance from myometrium (Taylor et al.), 987
excretion, effect of cholorothiazide on (Chesley and Uichanco), 467-472
radioactive, disappearance from uterine muscle in pregnancy (Weis, Bruns, and Taylor), 340
D-Sorbitol, absorption of vitamin B_{12} in pregnancy with reference to (Chow et al.), 91
South Atlantic Association of Obstetricians and Gynecologists, transactions of twentieth annual meeting, 699
twenty-year-old sectional society (Hutchinson), 699
Sperm drive, effect of body fluids on (Balin), 31
Spleen, rupture in pregnancy (Sparkman), 587
Squamous-cell carcinoma of cervix (*see* Carcinoma of cervix, squamous-cell)
Stalk, pituitary, section in goat, effects (Daniel and Pritchard), 1366 (Abst.)
Staphylococcal peritonitis in newborn (Beaven), 926 (Abst.)
Staphylococcus pyogenes infection, ward outbreak (Holland), 691 (Abst.)
Stein-Leventhal syndrome (Leventhal), 825
caution in diagnosis (Limage), 1368 (Abst.)
definition (Netter and Lambert), 1368 (Abst.)
surgical pathology (Plate), 1368 (Abst.)
Sterile couples, clinical studies (Johansson), 923 (Abst.)
Sterility, female, treatment with x-ray to pituitary and ovaries (Kaplan), 447 (Re-evaluation)
low-dosage irradiation of ovaries for, repudiation (Israel), 443 (Re-evaluation)
Steroid hormones, control over electrolyte balance (Barnes and Buckingham), 955
metabolism in human pregnancy (Davis and Plotz), 939
Stillbirth, bacteremic shock with Pseudomonas sepsis and (Pennisi, Lawrence, and Veprovsky), 1294
causes (Mirat and Wand), 461 (Abst.)
and irradiation (Kaplan), 450 (Re-evaluation)
Stress, effects on electrolyte balance (Barnes and Buckingham), 956
Stroke volume during uterine contraction (Hendricks), 977
Surgery, cardiac, associated with pregnancy (Winter et al.), 572
complications, 1201-1208
early postradiation, for endometrial carcinoma (Decker), 20
effects on electrolyte balance (Barnes and Buckingham), 956
general, as medical specialty (Taylor), 933
Surgical complications of pregnancy, 572-600
correction of congenital atresia of cervix (Rotter), 643
patient, hypothermia in (Barter, Albert, and Winshel), 1065
procedures, gynecological, 629-646
techniques, 1185-1200
Supension, uterine, and urinary stress incontinence (Hodgkinson and Kelly), 1114
Sweden, legal abortion in (Arén), 689 (Abst.)
Syntocinon in management of placental stage (Fugo and Dieckmann), 144
synthetic Pitocin (Reinberger and Mackey), 288
Syphilis, false positive serologic test for, in leprosy (King and Marks), 439

T

Teen-age dysmenorrhea, therapeutic exercises for (Golub et al.), 670
Tests, liver function, in pregnancy (Wetstone et al.), 480
Testosterone enanthate with estradiol valerate (Deladumone) for inhibition of lactation (Stein), 108
propionate, topical, in vulvar kraurosis-leukoplakia (Richardson and Williams), 791
Thecomatosis, estrogenic, in postmenopausal colporrhagia (Fienberg), 851
Thrombocytopenic purpura and eclampsia, pregnancy with (Salzberger and Koren), 1275
Thymol turbidity, serum, in pregnancy (Wetstone et al.), 484
Tissue culture determination of radiation sensitivity (Miller et al.), 1072
endometrial cells in, behavior (Papanicolaou and Maddi), 601
Toxemia(s) of pregnancy, articles on, 467-479, 1248-1278
cause of maternal death (Klein, Clahr, and Tamis), 1348
disappearance of radioactive sodium from myometrium and (Weis, Bruns, and Taylor), 340
fetal loss in (FitzGerald and Clift), 223 (Abst.)
and gout, clinical antagonism (Friedman and Little), 915
hypotensive drug therapy in (Dieckmann and Harrod), 374
hypothermic-hypotensive technique in (Barter, Albert, and Winshel), 1062
nasal mucus smear in (Abou-Shabanah), 1248
and placenta previa (Friedman and Little), 919 (Pertinent comments)
coexistence and symptomatology (Shanklin), 227 (Correspondence)
reply (Bieniarz), 227 (Correspondence)
pre-eclampsia and eclampsia, etiology (Browne), 220 (Abst.)
mild, Predema in (Patterson and Baer), 1265
psychophysiologic aspects (Salerno), 1268
in young primigravida (Poliakoff), 747
Toxemic pregnant women, uric acid metabolism in (Seitchik, Szutka, and Alper), 1151 (Re-evaluation)
Toxins, bacterial, in treatment of tumors, effects on normal and sarcoma 37-bearing mice (Donnelly, Havas, and Groesbeck), 460 (Abst.)
Toxoplasmosis (Thalhammer), 218 (B. rev.)
Transactions of American Gynecological Society, eighty-first annual meeting, 931
of Central Association of Obstetricians and Gynecologists, twenty-fifth annual meeting, 235
of South Atlantic Association of Obstetricians and Gynecologists, twentieth annual meeting, 699
Transfused sickle-trait cells, placental transfer (Macris, Hellman, and Watson), 1214
Transfusion, blood, role in treatment of hypofibrinogenemia (Pritchard), 359
placental (Lund and Sisson), 1019
Trichomonas vaginitis, mixture of antiseptic and local anesthetic for (Stewart et al.), 925 (Abst.)
new treatment (Giorlando and Brandt), 666

Trichomoniasis, vaginal, laboratory and clinical studies (Burch, Rees, and Kayhoe), 658
Trophoblast, histologic appearance, integrity of decidua correlated with (Speert), 491
Tubal fluid in reproductive process (Balin), 30
ligation, torsion of Fallopian tube following (Sandler), 41
pregnancy (*see* Pregnancy, tubal)
Tube (*see* Fallopian tube and tubal)
Tubes, Fallopian, role in sterility (Woltz et al.), 736
Tumor, adrenal cortical, consultation (Taylor and Ball), 1357 (Clinical problems)
Brenner, malignant, of ovary (Reel), 872
Wilms's, dystocia caused by (Copeland, Welburn, and West), 1329
Tumors, adenomatoid, of uterus and adnexa (Bolton and Hunter), 647
cervical, 1163-1175
mixed bacterial toxins in treatment (Donnelly, Havas, and Groesbeck), 460 (Abst.)
ovarian, 647-657, 851-882
estrogenic, in postmenopausal colporrhagia (Fienberg), 851
Twin tubal pregnancy, unilateral (Demick and Cavanagh), 533
Twins and cerebral palsy (Gingras et al.), 1367 (Abst.)
dizygotic, in unilateral tubal pregnancy (Demick and Cavanagh), 533
interlocked (Kreis and Miller), 1334

U

Umbilical cord, hematoma of (Breen, Riva, and Hatch), 1288
Unengaged vertex in nullipara at 38 weeks' gestation, significance (Burke, Rubin, and Berenberg), 132
Unicornuate uterus, postpartum inversion (McDuff and Keegan), 1299
Ureteral catheter, looped, in vesicovaginal fistula repair (Goodwin and Thelen), 641
obstruction in female child (Brack and Guild), 1105
Urethrovesicopubic relationships and stress incontinence (Hodgkinson and Kelly), 1114
Uric acid metabolism in pregnant women (Seitchik, Szutka, and Alper), 1151 (Re-evaluation)
Uricemia in gout and toxemia (Friedman and Little), 915
Urinary excretion of antidiuretic substances (Zuspan, Barnes, and Dillhoefer), 619
sediment in study of endocrinological disorders (Solomon, Panagotopoulos, and Oppenheim), 56
stress incontinence, urethrovesicopubic relationships and (Hodgkinson and Kelly), 1114
vaginal plastic operation for (Frankel), 1185
Urologic injuries in gynecology (Falk), 921 (B. rev.)
Urology as medical specialty (Taylor), 934
Uterine action, anomalies, and treatment (Kaern), 923 (Abst.)
contraction, hemodynamics (Hendricks), 969
decidua in ectopic pregnancy (Speert), 491
irritability, oxytocin-sensitivity test for (Smyth), 222 (Abst.)
polyp forceps and curettage (Javert), 61
suspension and urinary stress incontinence (Hodgkinson and Kelly), 1114
Uterovaginal prolapse, Manchester-Fothergill operation for (Conger and Keettel), 634
Uterus, adenomatoid tumors of (Bolton and Hunter), 647
contractions, and theory of labor (Goldfarb), 224 (Abst.)
didelphic, with carcinoma in situ of both cervices (Wall), 803
gravid, rupture (Ware, Jarrett, and Reda), 181
perforation by catheter (Speidel and Hatch), 558
pregnant, hematoma of rectus abdominis simulating rupture (Lucas and Baker), 1302
prolapse and inversion, cortisone induced (Fainstat), 53
rupture (Pedowitz and Perell), 161
at Boston Lying-in Hospital (Ferguson and Reid), 172
due to placenta accreta at site of previous cornual resection (Hogans and Friedman), 188
in late pregnancy and labor (Bancroft-Livingston and Myles), 690 (Abst.)
unicornuate, postpartum inversion (McDuff and Keegan), 1299

V

Vagina, carcinoma in situ, after hysterectomy for carcinoma in situ of cervix (May), 807
reconstruction with reversed seromuscular grafts (Shoemaker et al.), 1194
rupture of apex, after abdominal hysterectomy (Weisse, Watson, and Steffan), 1207
Vaginal bleeding, postmenopausal, problem of (Fienberg), 851
deliveries following cesarean section, analysis (Riva and Breen), 192
delivery after cesarean section (Ware, Jarrett, and Reda), 186
plastic operation for stress incontinence (Frankel), 1185
trichomoniasis, laboratory and clinical studies (Burch, Rees, and Kayhoe), 658
Vaginitis, articles on, 658-669
Trichomonas, laboratory and clinical studies (Burch, Rees, and Kayhoe), 658
new treatment (Giorlando and Brandt), 666
Vagisec, efficacy in Trichomonas vaginitis (Giorlando and Brandt), 666
Valve, urethral, cause of obstruction (Brack and Guild), 1110
Varicocele, pelvic, diagnosis by phlebography (Topolanski-Sierra), 47
Vascular aspects of uterine contraction (Hendricks), 969
Vasoconstriction, digital, in pregnancy (Mendlowitz, Altcheck, and Naftchi), 473
Venereal disease, Trichomonas vaginitis as (Giorlando and Brandt), 666
Venous pressure changes during uterine contraction (Hendricks), 977
in newborn infant, study (Parkinson), 461 (Abst.)
Ventricular fibrillation with hypothermia (Barter, Albert, and Winshel), 1066
Vertex, unengaged, in nullipara at 38 weeks' gestation, significance (Burke, Rubin, and Berenberg), 132
Vesicovaginal fistula, looped ureteral catheter in repair (Goodwin and Thelen), 641
Virilization, varying severity, in adrenogenital syndrome (Wilson and Keating), 394
Vitamin B_{12}, absorption in human pregnancy with reference to effect of D-sorbitol (Chow et al.), 91
Voorhees bag and intrauterine bougie, present status (Taylor), 553

Vulvar disease, benign, vulvectomy for (Collins et al.), 363
kraurosis-leukoplakia, topical testosterone in (Richardson and Williams), 791
Vulvectomy for benign vulvar disease (Collins et al.), 363

W

Ward outbreak of *Staphylococcus pyogenes* infection (Holland), 691 (Abst.)
Wastage, fetal (Steer), 563
Weight estimation, fetal (McSweeney), 1279
Wilms's tumor, dystocia caused by (Copeland, Welburn, and West), 1329
Wounds, healing (Williamson), 687 (B. rev.)

X

X-ray, lateral, in dystocic labors (Roberts et al.), 1306
pelvimetry and outcome of labor (Steer), 118
single, to exclude placenta previa (Earn, Freer, and Cairns), 926 (Abst.)
therapy of female sterility directed to pituitary and ovaries (Kaplan), 447 (Re-evaluation)
treatment of puerperal mastitis (Grasberger and Zeiss), 226 (Abst.)

Y

Youth, role in pre-eclampsia (Salerno), 1272

D

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CONTENTS

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GYNECOLOGY

Cervical Tumors

COLPOMICROSCOPY: ITS VALUE IN THE MICROSCOPIC EXAMINATION OF THE UTERINE CERVICAL EPITHELIUM IN VIVO
Louis A. Wolfe, M.D., New York, N. Y. 1163

SARCOMA BOTRYOIDES
Theodore R. Miller, M.D., New York, N. Y. 1172

Endometriosis

RADIOGRAPHIC FEATURES OF RECTOSIGMOID ENDOMETRIOSIS
Gordon J. Culver, M.D., Rubens Marcondes Pereira, M.D., and Roy Seibel, M.D., Buffalo, N. Y. 1176

Surgical Techniques

FULL-THICKNESS ANTERIOR COLPORRHAPHY FOR CORRECTION OF URINARY STRESS INCONTINENCE
Donald S. Frankel, M.D., Philadelphia, Pa. 1185

RECONSTRUCTION OF THE VAGINA OF DOGS WITH REVERSED SEROMUSCULAR GRAFTS
William C. Shoemaker, M.D., Boston, Mass., Mark A. Blatt, M.D., Charles E. Pohl, M.D., and Paul J. Grotzinger, M.D., Philadelphia, Pa. 1194

Complications of Surgery

PROLONGED LEVARTERENOL BITARTRATE (LEVOPHED) THERAPY IN SHOCK FOLLOWING REMOVAL OF A LARGE OVARIAN NEOPLASM
Ronald Dew, M.D., Columbia, S. C. 1201

NEUROFIBROMA FOLLOWING PRESACRAL NEURECTOMY
Ira S. Goldenberg, M.D., and Donald B. Alderman, M.D., New Haven, Conn. . 1204

TRAUMATIC RUPTURE OF THE APEX OF THE VAGINA TWENTY MONTHS FOLLOWING ABDOMINAL HYSTERECTOMY
Harris A. Weisse, M.D., Mark Watson, M.D., and Lloyd J. Steffan, M.D., Plymouth, Wis. 1207

OBSTETRICS

Function of Placenta and Amnion

THE PERMEABILITY OF THE RABBIT PLACENTA TO HOMOLOGOUS ALBUMIN
Edward G. Winkler, M.D., James G. Fitzpatrick, M.D., and James J. Finnerty, M.D., Buffalo, N. Y. 1209

THE TRANSMISSION OF TRANSFUSED SICKLE-TRAIT CELLS FROM MOTHER TO FETUS
Nicholas T. Macris, M.D., Louis M. Hellman, M.D., and R. J. Watson, M.D., Brooklyn, N. Y. 1214

contents . . .

continued from page 1

FREE AMINO ACIDS IN HUMAN AMNIOTIC FLUID, FETAL AND MATERNAL SERUM
Zolton T. Wirtschafter, M.D., Portland, Ore. 1219

THE OXYGEN TENSION OF THE AMNIOTIC FLUID
Sven Sjöstedt, M.D., Gösta Rooth, M.D., and Franco Caligara, Ph.D., Lund, Sweden 1226

Abnormal Pregnancy

PROLONGED PREGNANCY SYNDROME
James Walker, B.Sc., M.D., F.R.C.O.G., Dundee, Scotland 1231

Toxemia of Pregnancy

THE NASAL MUCUS SMEAR IN TOXEMIAS OF PREGNANCY
E. Himmat Abou-Shabanah, M.D., J. G. Boutselis, M.D., W. J. Frajola, Ph.D., and J. C. Ullery, M.D., Columbus, Ohio 1248

EVALUATION OF A DIURETIC SUBSTANCE IN THE MANAGEMENT OF MILD PRE-ECLAMPSIA
Rushton E. Patterson, M.D., and Harry Baer, M.D., Memphis, Tenn. 1264

PSYCHOPHYSIOLOGIC ASPECTS OF THE TOXEMIAS OF PREGNANCY
Louis J. Salerno, M.D., New York, N. Y. 1268

PREGNANCY ASSOCIATED WITH THROMBOCYTOPENIC PURPURA AND ECLAMPSIA
Maccabi Salzberger, M.D., and Zev Koren, M.D., Jerusalem, Israel 1275

Fetus

FETAL WEIGHT ESTIMATION
Daniel J. McSweeney, M.D., Boston, Mass. 1279

PROLONGED RETENTION OF A DEAD FETUS
Robert E. Wheatley, M.D., San Mateo, Calif. 1283

THE EFFECTS OF ORALLY ADMINISTERED RH HAPTEN
Bettina B. Carter, Ph.D., and A. Franklyn Lewis, M.S., Kalamazoo, Mich. . . . 1285

HEMATOMA OF THE UMBILICAL CORD
J. L. Breen, Captain, MC, USA, H. L. Riva, Colonel, MC, USA, and R. P. Hatch, Captain, MC, USA 1288

Complications of Pregnancy

APPENDICITIS DURING PREGNANCY
Warner M. Soelling, M.D., Modesto, Calif. 1291

BACTEREMIC SHOCK ASSOCIATED WITH PSEUDOMONAS SEPSIS AND STILLBIRTH
Joseph A. Pennisi, M.D., George J. Lawrence, Jr., M.D., and Edward C. Veprovsky, M.D., Flushing, N. Y. 1294

POSTPARTUM INVERSION OF A UNICORNUATE UTERUS
Henry C. McDuff, Jr., M.D., and James Keegan, M.D., Providence, R. I. . . . 1299

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contents . . .

continued from page 2

Hematoma of the Rectus Abdominis Muscle Simulating Rupture of the Pregnant Uterus
William E. Lucas, Lieutenant (MC) USN, and William S. Baker, Jr., Captain (MC) USN 1302

Management of Labor

Intrapartum Lateral X-ray in the Conduct of Dystocic Labors
Leonard M. Roberts, M.D., Jack J. Squire, M.D., Alan F. Guttmacher, M.D., and Richard Marshak, M.D., New York, N. Y. 1306

Dystocia and Occipitoposterior
Leroy R. Weekes, M.D., and Kenneth G. Hobbs, Jr., M.D., Los Angeles, Calif. . 1314

The Use of Glutethimide in the Labor Patient
Lester R. Graves, Jr., M.D., Memphis, Tenn. 1324

Dystocia Caused by Wilms's Tumor
L. V. Copeland, M.D., J. C. Welburn, M.D., and O. T. West, M.D., Fairfield, Ala. 1329

Interlocked Twins
David J. Kreis, M.D., and Robert T. Miller, M.D., New Haven, Conn. 1334

Labor Following Severe Thermal Burns
Nejdat Mulla, M.D., Albuquerque, N. Mex. 1338

Maternal Mortality

Classification and Analysis of Maternal Deaths in Bronx County, New York, 1946-1957
Milton D. Klein, M.D., Jacob Clahr, M.D., and Abraham B. Tamis, M.D., New York, N. Y. 1342

DEPARTMENT OF CURRENT OPINION

Clinical Problems

Adrenal Cortical Tumor 1357
Missed Abortion 1361

REVIEWS AND ABSTRACTS

Reviews of New Books 1364
Books Received 1366
Selected Abstracts 1366

CORRESPONDENCE

Correspondence 1372

INDEX

Index 1373

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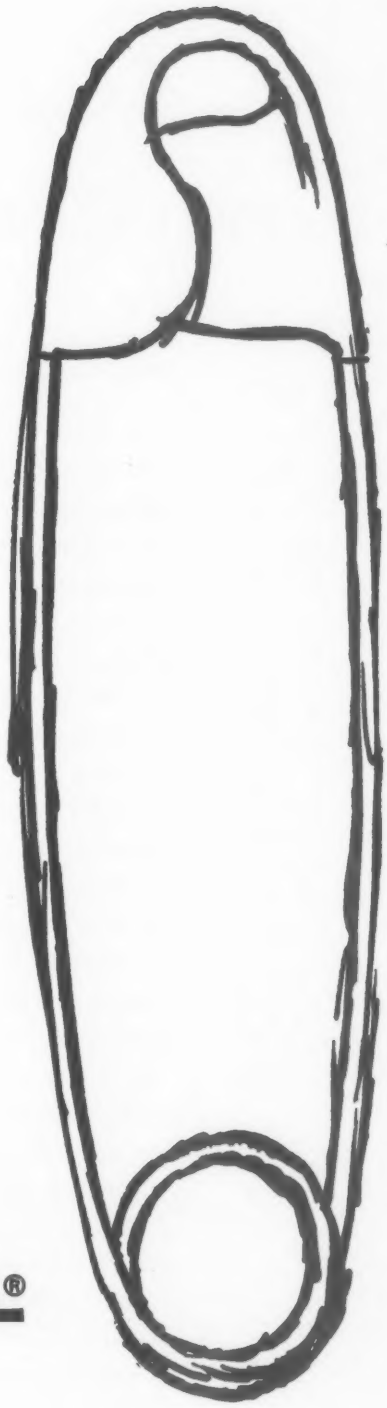

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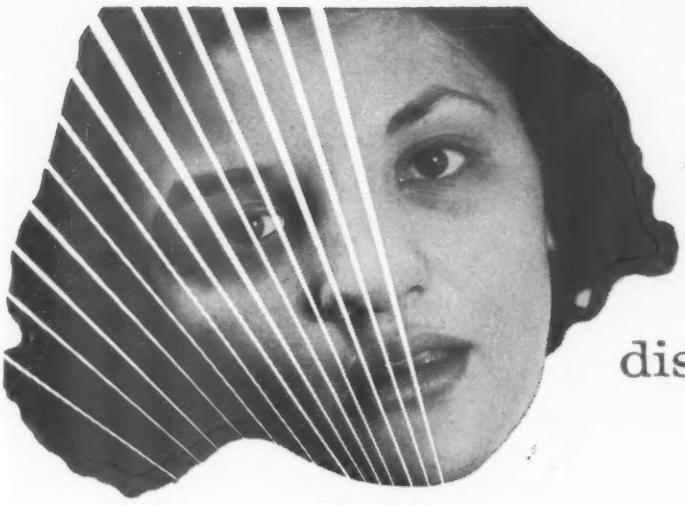

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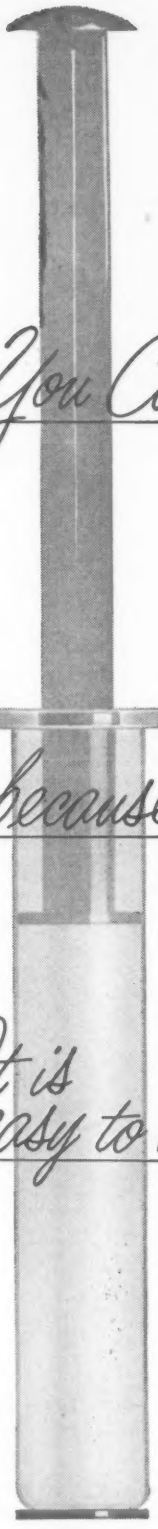

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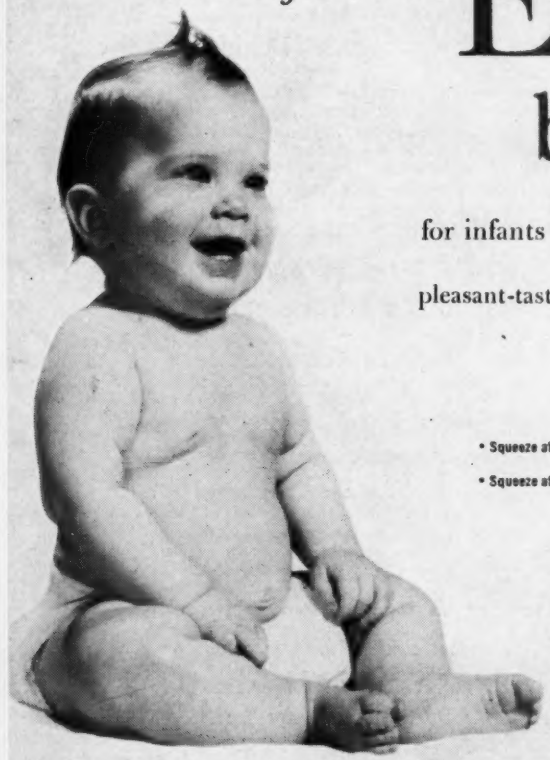

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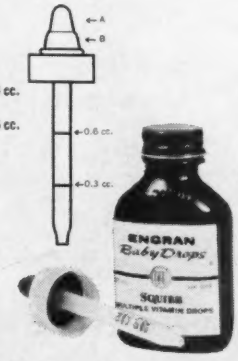

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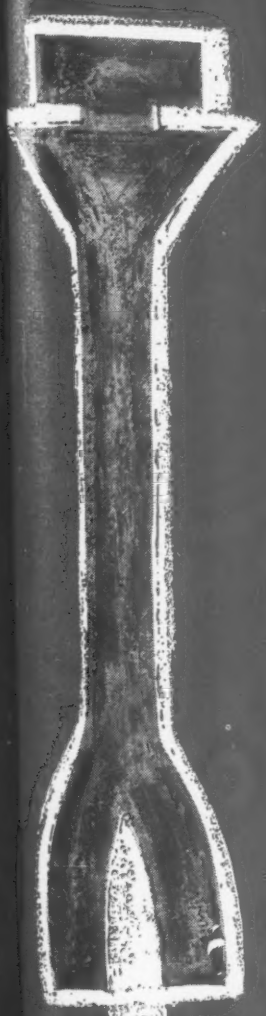

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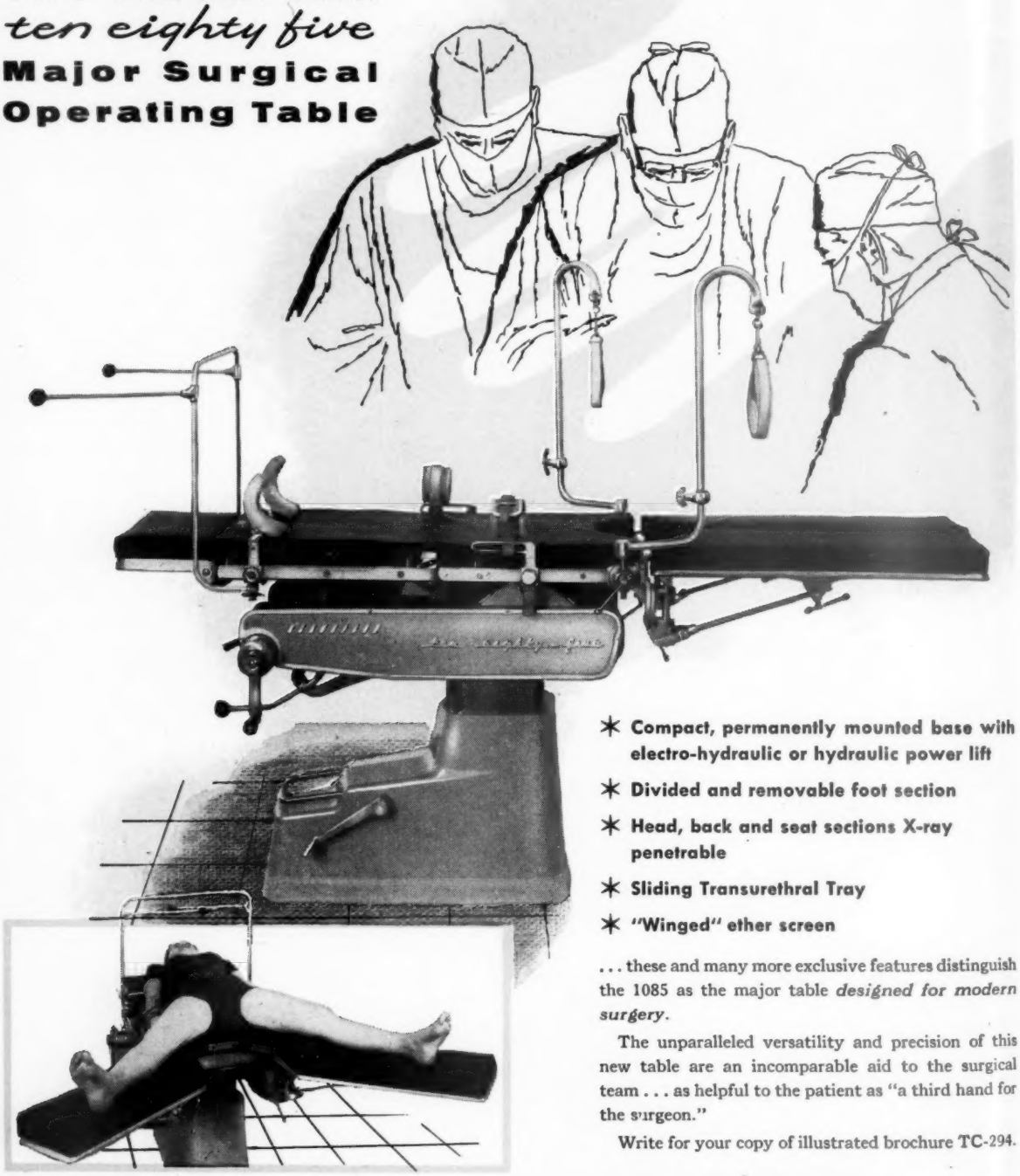

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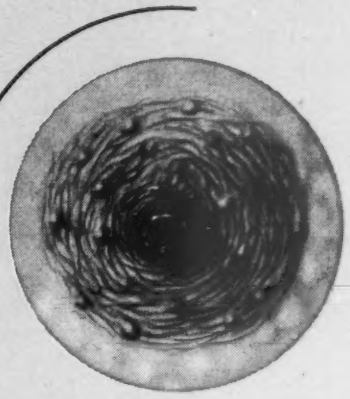

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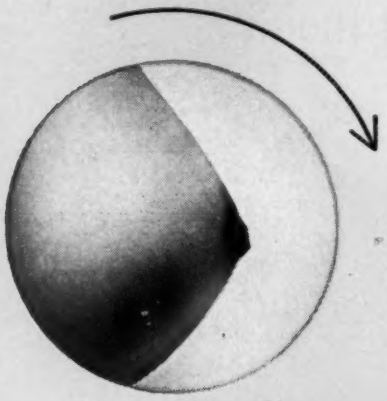

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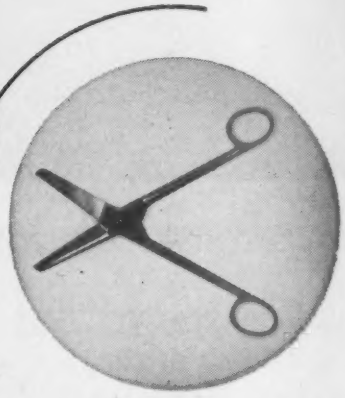

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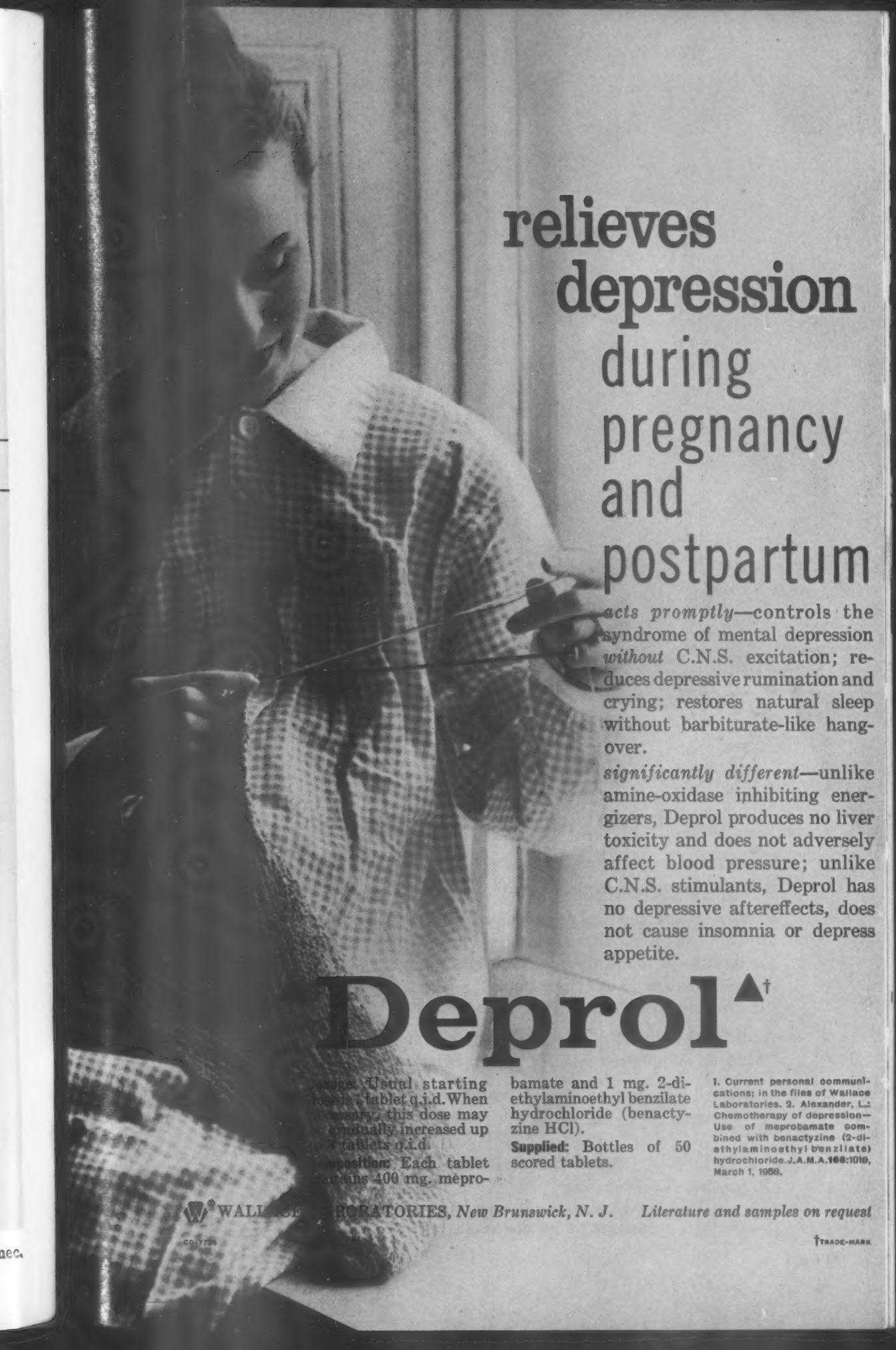

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significantly different—unlike amine-oxidase inhibiting energizers, Deprol produces no liver toxicity and does not adversely affect blood pressure; unlike C.N.S. stimulants, Deprol has no depressive aftereffects, does not cause insomnia or depress appetite.

Deprol▲†

...ge: Usual starting ...tablet q.i.d. When ...ssary, this dose may ...ndually increased up ...tablets q.i.d.

...position: Each tablet ...ains 400 mg. meprobamate and 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl).

Supplied: Bottles of 50 scored tablets.

1. Current personal communications; in the files of Wallace Laboratories. 2. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958.

WALL...E ...BORATORIES, *New Brunswick, N. J.* *Literature and samples on request*

CO-7726

†TRADE-MARK

All are in the picture . . .

baby, mother, and physician

S-M-A provides adequate nutrition for normal health and growth.

S-M-A Service* . . . A specialized program designed to complement the instructions of the physician from the first visits of the expectant mother through the months of infant feeding. The Service includes the beautifully illustrated and informative "Your Baby Book"; a personalized Mother's Gift from you; "Instructions for Care of Mother and Baby."

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*Available without charge from your Wyeth Territory Manager for all obstetrical patients in your practice.

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is rare in any human endeavor. When it appears, it may be perceived in various forms—as a work of art, a discovery, an idea, or an achievement of scientific inquiry. The outward form is incidental, but the intrinsic quality is readily recognized....

To partake of the quality of greatness, a therapeutic preparation must first of all achieve a degree of universality...the cumulative experience of thousands of physicians over a period of many years. From this experience, then, is born that unhesitating confidence which may be summed up in the term "drug of choice."

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ROCHE—Reg. U. S. Pat. Off. GANTRISIN®—brand of sulfisoxazole

A brighter "Good morning, doctor!"

No complaints about

* post-episiotomy,
* tender hemorrhoids,
* or fissured nipples when you prescribe

Americaine® Topical Anesthetic

Americaine relieves surface discomfort quickly, sustains relief up to six hours with a single application—because only Americaine contains 20% dissolved benzocaine.

What about sensitivities? None reported in over 11,800 published clinical cases[1]...negligible incidence in 10 years' steadily growing use.

Americaine Aerosol

For quick spray application. Available in 3 oz. prescription size, and 5.5 oz. and 11 oz. dispensers.

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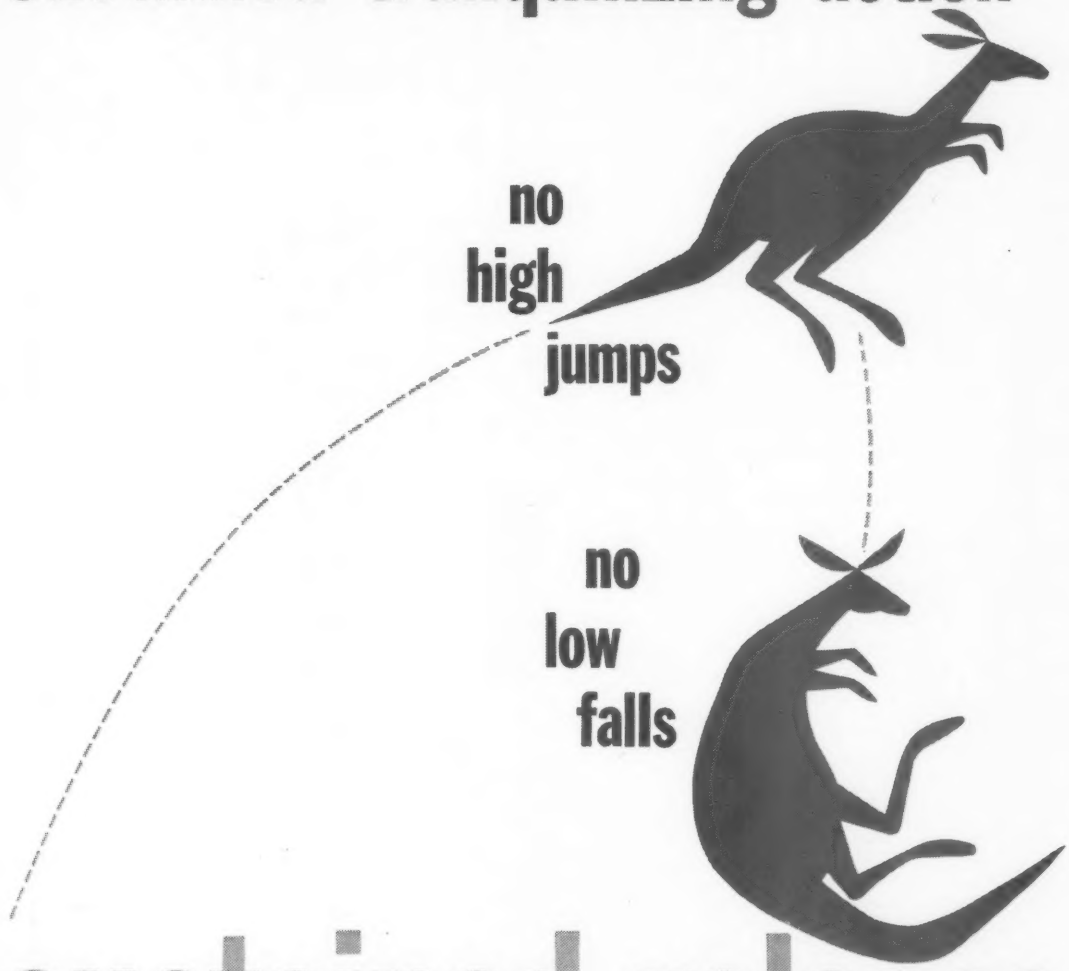
For simple manual application. Available in 1 oz. tube w/applicator.

1. References on request.

ARNAR-STONE LABORATORIES, INC., *Mount Prospect, Ill.*

Sustained tranquilizing action



sustained release

Meprospan*

meprobamate (Miltown®) capsules

q. 12 h.

effectively relieve nervous tension and anxiety without interruption, **day and night.** Two capsules on arising last **all day,** two capsules at bedtime last **all night.** *Exceptionally well tolerated . . . extremely convenient.*

Dosage: 2 Meprospan capsules q. 12 h.
Supplied: 200 mg. capsules, bottles of 30.

Literature and samples on request

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who discovered and introduced Miltown®

Reference: Baird, H. W., III: A comparison of Meprospan (sustained action meprobamate capsule) with other tranquilizing and relaxing agents in children. Submitted for publication, 1958.

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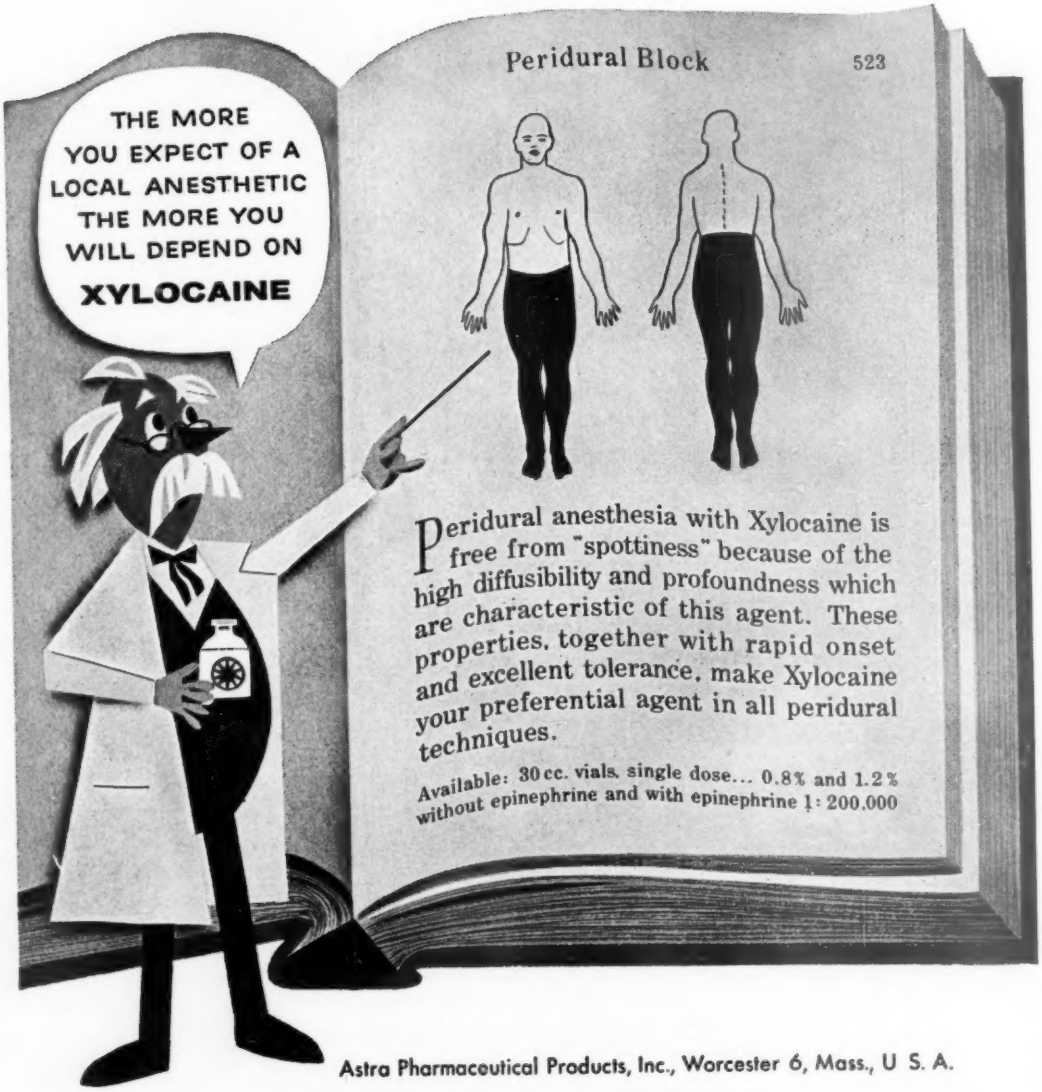
peridural anesthesia without "spottiness"


THE MORE YOU EXPECT OF A LOCAL ANESTHETIC THE MORE YOU WILL DEPEND ON XYLOCAINE
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Peridural anesthesia with Xylocaine is free from "spottiness" because of the high diffusibility and profoundness which are characteristic of this agent. These properties, together with rapid onset and excellent tolerance, make Xylocaine your preferential agent in all peridural techniques.
Available: 30 cc. vials, single dose... 0.8% and 1.2% without epinephrine and with epinephrine 1:200,000

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ASTRA

XYLOCAINE® HCl

(brand of lidocaine*)

Sterile solution for injection

SEE PDR

*U S. Pat No 2,441,498 Made in U S A.

Emphasizing the *PREOPERATIVE* use of

Adrenosem®* SALICYLATE

(Brand of carbazochrome salicylate)

TO CONTROL OOZING AND BLEEDING

FOR THE CHILD PATIENT BEFORE AND AFTER ADENOIDECTOMY AND TONSILLECTOMY:

"1. Preoperative medication: For seven days before operation Adrenosem, in doses of 1 mg., was administered three times a day and a mixture of benzathine penicillin and triple sulfonamides, in doses of 1 teaspoonful three times a day."[1]

"On the day of operation, Adrenosem 5 mg. hypodermically is administered to minimize capillary bleeding."[2]

FOR ALL PATIENTS BEFORE LARYNGOLOGIC, BRONCHOSCOPIC AND ESOPHAGOLOGIC PROCEDURES:

"The routine preoperative use of Adrenosem in tonsil and adenoid surgery diminishes both the bleeding at the time of operation and the oozing in the immediate postoperative period."[3]

IN UROLOGICAL PROCEDURES:

"My own method is, after ensuring maximum haemostasis, to employ every known means of ensuring that clotting shall occur, viz. the use of (1) Oxycel, (2) adrenalin with procaine locally into prostatic capsule, (3) Adrenosem systemically . . ."[4]

IN PLASTIC SURGERY:

". . . this drug [Adrenosem Salicylate] is a valuable aid to plastic surgery in its ability to reduce blood loss and provide a clearer operative field."[5]

IN ORAL SURGERY:

"The difference in the control bleeding time and the bleeding time after the administration of 10 mg., intramuscularly or orally, of Adrenosem Salicylate was statistically significant."[6]

"No postoperative bleeding was noticed in those patients who had received Adrenosem Salicylate preoperatively."[7]

IN PATIENTS WITH BLEEDING DISTURBANCES:

"Treatment consisted of the administration of Adrenosem® Salicylate intramuscularly in quantities from 20 to 80 mg. over a period of four to eight days before operation."[8]

NON-TOXIC, NO CUMULATIVE EFFECT:

"Adrenosem Salicylate is non-toxic and has a high index of therapeutic safety. At the recommended dosage levels there are no contraindications. It has no cumulative effect. Patients treated for more than two years show no toxic effects attributable to the drug."[9]

*U.S. Pat. 2581850,2506294

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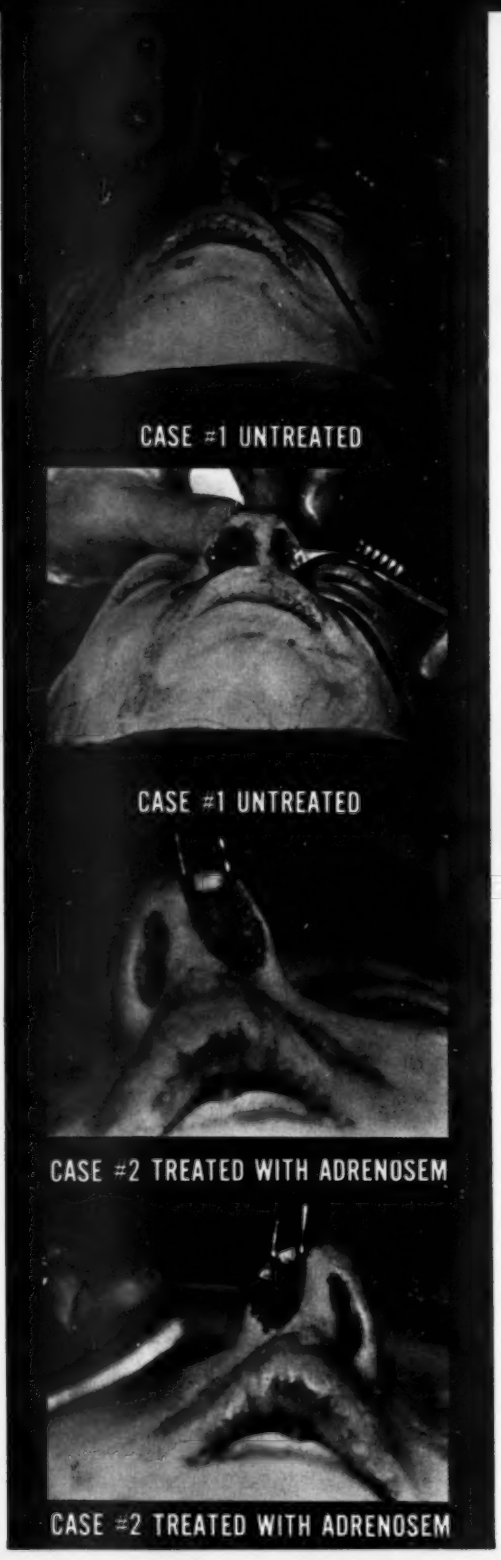

effective *preoperatively* in virtually every operative procedure

TO CONTROL OOZING AND BLEEDING

Adrenosem®

SALICYLATE

(Brand of carbazochrome salicylate)

The photographs to the left show the same rhinoplastic procedure on two patients—one untreated, one treated with Adrenosem.

Adrenosem is supplied: Ampuls, 1 cc., 5 mg.; Tablets, 1 and 2.5 mg.; Syrup, each 5 cc., 2.5 mg. Potency of all dosage forms stated in terms of the active ingredient, adrenochrome monosemicarbazone.

Write for literature describing the action and uses of Adrenosem Salicylate.

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1. Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, N.Y. State J. Med. 56:886 (Mar., 1956).

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5. Brown, W.S.: The Use of Adrenosem Salicylate to Control Postoperative Bleeding in Plastic Surgery: Dermabrasion, Northwest Med. 57:470 (Apr., 1958)

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Vaginal Cream

promotes proliferation and
vascularity of the vaginal mucosa in
postmenopausal patients, and used

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tends to restore the integrity
of atrophied, friable tissues, and
change the vaginal environment to one
that resists infection, which

facilitates surgery—favors healing

Applied for 7 to 10 days before, and for 10 days after plastic vaginal surgery in the postmenopausal patient, "Premarin" Vaginal Cream effectively revitalizes the vaginal epithelium making the intervention less difficult and accelerating healing. It is also widely prescribed for the prompt relief of senile vaginitis and pruritus vulvae, as well as juvenile vaginitis. Also available with hydrocortisone as "Premarin" H-C Vaginal Cream for use when immediate anti-inflammatory, antipruritic action is indicated, particularly in the initial stages of estrogen therapy of various vulvovaginal disorders.

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5862

quick, accurate early pregnancy diagnosis...

new,

3-day oral test

for pregnancy

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anhydrohydroxyprogesterone 50.00 mg.
activated by ethinyl estradiol 0.03 mg. } per tablet

safe . . . . . physiologic . . . . . therapeutic

Pregnancy may now be diagnosed safely, simply and accurately in its earliest weeks by oral administration of PRO-DUOSTERONE® tablets four times daily—with each meal and at bed time—for only three consecutive days. In the nonpregnant patient uterine bleeding usually occurs 3 to 7 days after progesterone therapy.[1] No bleeding occurs when pregnancy exists; on the contrary, gestation is protected.[2] Moreover, in short-term functional amenorrhea regular menstrual cycles are usually restored by oral progestogen.[1]

The speed and precision of this oral diagnostic test are unsurpassed, and "no laboratory equipment, animals, or specimens are needed."[1] The 3-day, oral PRO-DUOSTERONE test for pregnancy is also less costly than biologic methods. Finally, full diagnostic and therapeutic efficiency is assured by the small estrogen component of the PRO-DUOSTERONE formula since "Progesterone has no action whatsoever in the absence of estrogens."[3] Supplied: Bottles of 24 pink tablets. **Roussel Corporation,** 155 East 44th Street, New York 17, New York.

1. Hayden, G. E.: Am. J. Obs. & Gynec. *76*:271, 1958. 2. New & Nonofficial Drugs: J.A.M.A. *168*:181, 1958. 3. Page, E. W.: GP *9*:53, 1954.

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IN URTICARIA AND PRURITUS

VISTARIL*

HYDROXYZINE PAMOATE

A PSYCHOTHERAPEUTIC ANTIHISTAMINE

(as designated by A.M.A. Council on Drugs, 1958)

SPECIFIC ANTIHISTAMINIC ACTION in the treatment of a variety of skin disorders commonly seen in your practice.

"While some of the tranquilizers are only partially effective as far as antiallergic activities are concerned... [hydroxyzine] has been found, by comparison, to be the most potent thus far . . ."[1]

"The most striking results were seen in those patients with chronic urticaria of undetermined etiology."[2]

PLUS

PSYCHOTHERAPEUTIC POTENCY for the relief of anxiety and tension.

The psychotherapeutic effectiveness of hydroxyzine (VISTARIL) was confirmed in a series of 479 patients suffering from a wide variety of dermatoses, including atopic dermatitis, neurodermatitis, psoriasis, lichen planus, nummular eczema, dyshidrosis, pruritus ani and vulvae, and rosacea. "Adverse reactions were minimal."[3]

RECOMMENDED ORAL DOSAGE: *50 mg. q.i.d. initially; adjust according to individual response.*

VISTARIL Capsules: *25 mg., 50 mg., 100 mg.*
VISTARIL Parenteral Solution: *10 cc. vials and 2 cc. Steraject® Cartridges. Each cc. contains 25 mg. hydroxyzine (as the HCl).*

More than a tranquilizer

REFERENCES:
1. Eisenberg, B. C.: Clinical Medicine *5*:897-904 (July) 1958.
2. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958.
3. Robinson, H. M., et al.: So. Med. J. *50*:1282 (Oct.) 1957.

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Now
in inflammatory anorectal disorders . . .

The Promise of Greater Relief

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hydrocortisone for effective control of proctitis

- Proctitis accompanying ulcerative colitis
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- Postoperative scar tissue with inflammatory reaction
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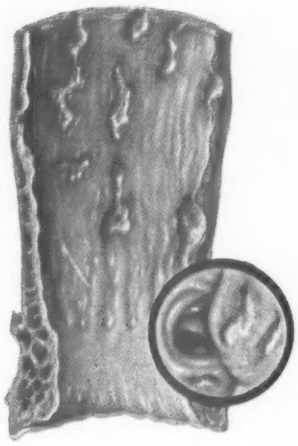
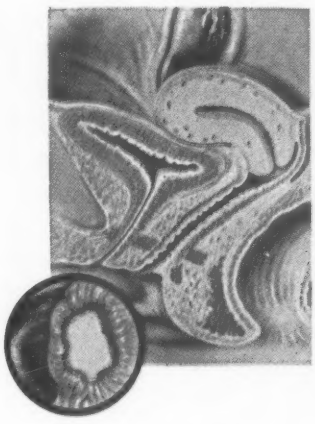
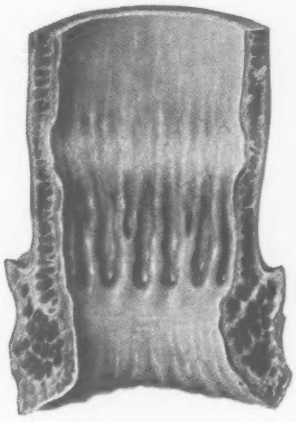


Ulcerative Colitis



Radiation Proctitis



Postoperative Scar Tissue

Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

Wyanoids® HC

Rectal Suppositories with Hydrocortisone, Wyeth

Wyeth®
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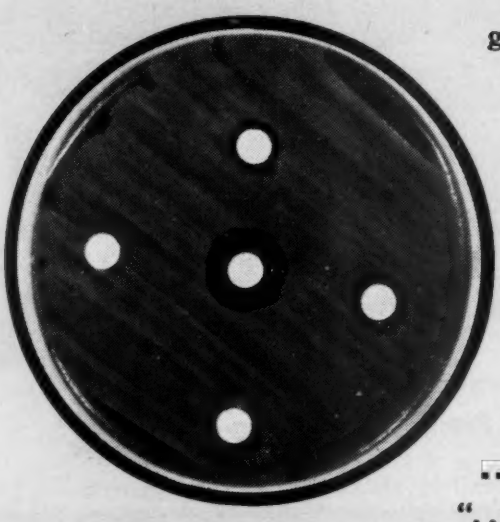
on the problem of

A POINT OF VIEW IN '55

"At this time, it appears that the problem of antibiotic-resistant bacteria is the greatest fear in the future with chronic infections of the . . . urinary tract . . ."[1]



A POINT OF FACT IN '58

". . . This prediction has proved to be correct for both gram-positive and gram-negative organisms."[2]

. . . WITH ONE NOTABLE EXCEPTION

". . . studies indicate that microorganisms, in vitro and in vivo, do not appear to develop resistance to FURADANTIN."[3]

antibiotic-resistant bacteria

for acute and chronic genitourinary tract infections

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brand of nitrofurantoin

AVERAGE FURADANTIN DOSAGE: In acute, complicated or refractory cases and in chronic infections—100 mg. q.i.d., with meals and with food or milk on retiring.

REFERENCES: 1. Flippin, H. F.: Virginia M. Month. 82:435, 1955. 2. Caswell, H. T., et al.: Surg. Gyn. Obst. 106:1, 1958. 3. Nesbitt, R. E. L., Jr., and Young, J. E.: Obst. Gyn., N. Y. 10:80. 1957.

in 7 years—negligible development of bacterial resistance with FURADANTIN

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*Ford, R.V., and Moyer, J.H.: Rauwolfia Toxicity in the Treatment of Hypertension, Postgrad. Med. *23*:41 (Jan.) 1958.

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ALSEROXYLON, 1 MG.

virtually free from side actions

just two tablets at bedtime

After full effect one tablet suffices

Enhances safety when more potent drugs are needed.

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alseroxylon 1 mg. and alkavervir 3 mg.
for moderate to severe hypertension.
Initial dose, 1 tablet t.i.d., p.c.

Rauwiloid® + Hexamethonium
alseroxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.
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Both combinations in convenient single-tablet form.

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need

iron therapy?

Many clinicians agree that the normal woman of child-bearing age requires iron therapy for a month or six weeks of *each* year.

Iron-deficiency anemia, usually identified as hypochromic microcytic anemia, is seen in most age groups, from the adolescent to the senior members.

For the treatment of these common anemias, Livitamin offers *peptonized* iron—virtually predigested, well absorbed, and less irritating than other forms. The Livitamin formula, which contains the B complex, provides integrated therapy to normalize the blood picture.

Formula: Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} Activity (derived from Cobalamin conc.)	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

LIVITAMIN®

with Peptonized Iron

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— *look to peptonized iron*

CURRENT STUDIES* SHOW PEPTONIZED IRON

One-third as toxic as ferrous sulfate.

Absorbed as well as ferrous sulfate.

Non-astringent.

Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)

More rapid response in iron-deficient anemias.

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition *1*:35 (Jan.-Feb., 1957).

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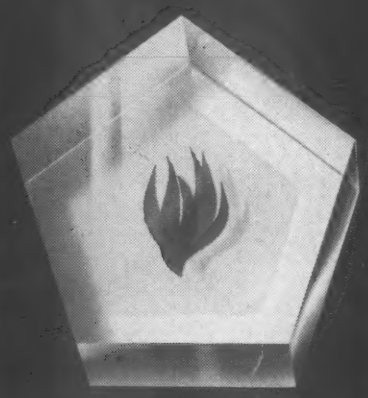
a new order of magnitude in corticosteroid therapy!

The great corticosteroid era opened ten years ago with the introduction of Cortone® (Cortisone). Today, MERCK SHARP & DOHME proudly presents the crowning achievement of the first corticosteroid decade—DECADRON (dexamethasone)—a new and unique compound, which brings a new order of magnitude to corticosteroid therapy.



Decadron*

DEXAMETHASONE

to treat more patients more effectively

MSD

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PENNSYLVANIA

a new order of magnitude

in anti-inflammatory potency

DECADRON "possesses greater anti-inflammatory potency per milligram than any steroid yet produced,"[1] and is "the most potent steroid thus far synthesized."[2] Milligram for milligram, it is, on the average, 5 times more potent than 6-methylprednisolone or triamcinolone; 7 times more potent than prednisone; 28 times more potent than hydrocortisone; and 35 times more potent than cortisone.

in dosage reduction

Thanks to this unprecedented potency, DECADRON is "highly effective in suppressing the manifestations of rheumatoid arthritis when administered in remarkably small daily milligram doses."[3] In a number of cases, doses as low as 0.5-0.8 mg. proved sufficient for daily maintenance. The average maintenance dosage in rheumatoid arthritis is about 1.5 mg. daily.

in elimination and reduction of side effects

Virtual **absence of diabetogenic activity, edema, sodium or water retention, hypertension, or psychic reactions** has been noted with DECADRON.[1,2,3,4] Other "classical" reactions were less frequent and less severe. DECADRON showed no increase in ulcerogenic potential, and **digestive complaints were rare. Nor have there been any new or "peculiar" side effects,** such as muscle wasting, leg cramps, weakness, depression, anorexia, weight loss, headache, dizziness, tachycardia, or erythema. Thus DECADRON introduces **a new order of magnitude in safety,** unprecedented in corticosteroid therapy.

in therapeutic effectiveness

With DECADRON, investigators note "a decided intensification of the anti-inflammatory activity"[3] and antirheumatic potency.[4] Clinically, this was manifested by a **higher degree of improvement** in many patients previously treated with prednisteroids,[3] and by **achievement of satisfactory control in an impressive number of recalcitrant cases.**[3,4]

in therapeutic range

More patients can be treated **more effectively** with DECADRON. Its higher anti-inflammatory potency frequently brings relief to cases resistant to other steroids. Virtual freedom from diabetogenic effect in therapeutic dosage permits treatment of many diabetics without an increase in insulin requirements. Absence of hypertension and of sodium and fluid retention allows effective therapy of many patients with cardiovascular disorders. Reduction in the incidence and severity of many side effects extends the benefits of therapy to numerous patients who could not tolerate other steroids. And a healthy sense of well-being, reported by nearly all patients on DECADRON, assures greater patient cooperation.

References:
1. Boland, E. W.: California Med. 88:417 (June) 1958. 2. Bunim, J. J., et al.: Arthr. & Rheum. 1:313 (Aug.) 1958 3. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., June 21, 1958, San Francisco, Calif. 4. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., June 21, 1958, San Francisco, Calif.

DEXAMET

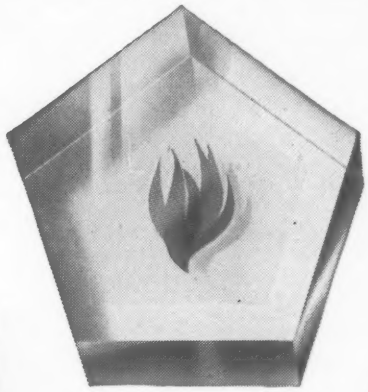
To treat more patients more effectively in all allergic and inflammatory disorders amenable to corticosteroid therapy

DOSAGE AND ADMINISTRATION
With proper adjustment of dosage, treatment may ordinarily be changed over to DECADRON from any other corticosteroid on the basis of the following milligram equivalence:

One 0.75 mg. tablet of Decadron* (dexamethasone) replaces:

one 4 mg. tablet of	one 5 mg. tablet of	one 20 mg. tablet of	one 25 mg. tablet of
methylprednisolone or triamcinolone	prednisolone or prednisone	hydrocortisone	cortisone

SUPPLIED:
As 0.75 mg. scored pentagon-shaped tablets; also as 0.5 mg. tablets, to provide maximal individualized flexibility of dosage adjustment.



Decadron*

DEXAMETHASONE

Detailed literature on DECADRON is available to physicians on request.

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The great corticosteroid era opened ten years ago with the introduction of Cortone® (Cortisone). Today, MERCK SHARP & DOHME proudly presents the crowning achievement of the first corticosteroid decade—DECADRON (dexamethasone)—the new and unique compound, which brings a new order of magnitude to corticosteroid therapy.

Decadron*

DEXAMETHASONE

to treat more patients more effectively

MSD MERCK SHARP & DOHME

after baby is born

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Made from whole milk and Dextri-Maltose. A "classic" modified milk formula, of the type used successfully over the years in feeding millions of babies.

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Sobee,® Nutramigen,® Probana,® Lofenalac (new low phenylalanine formula).

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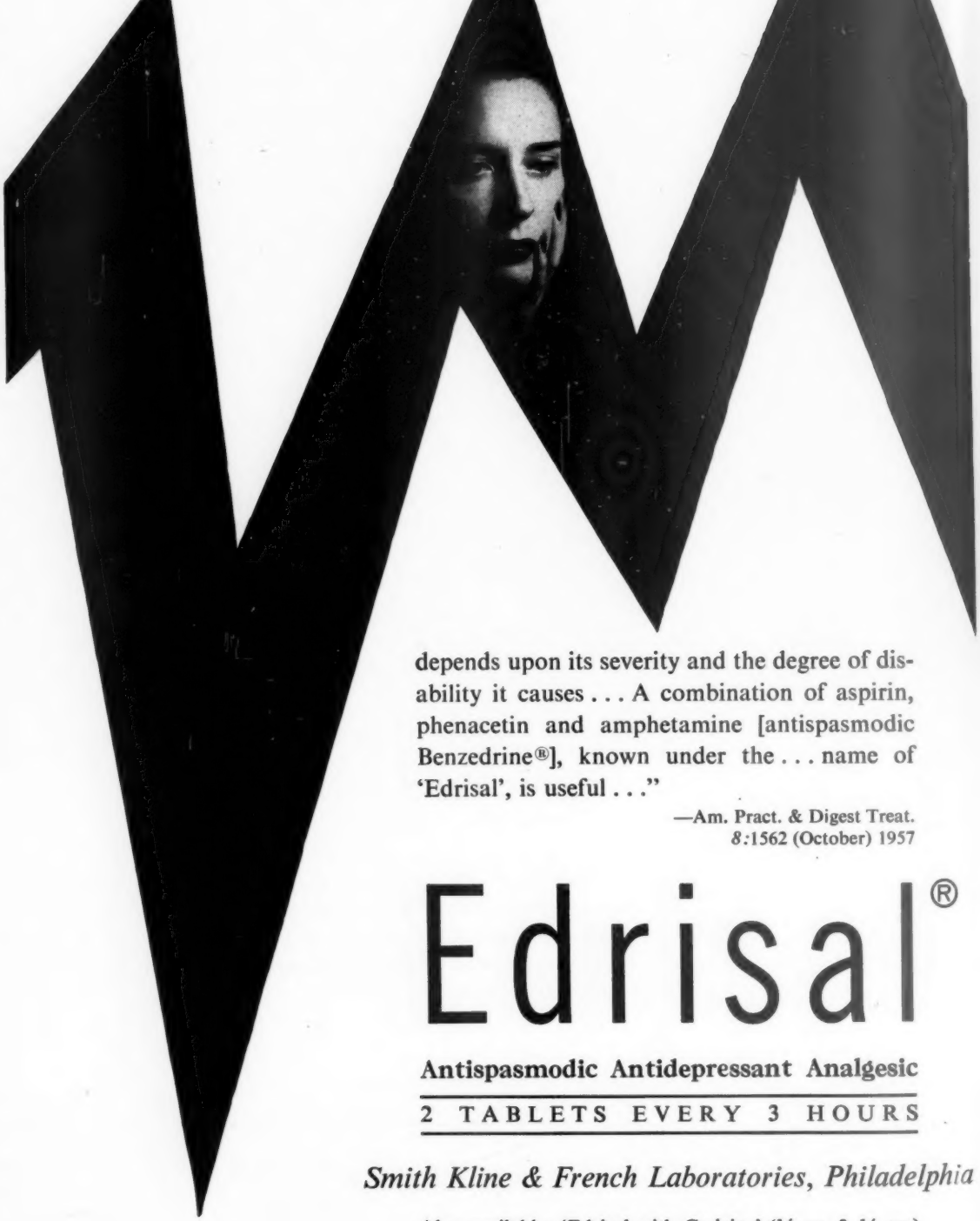
"The treatment of spasmodic dysmenorrhea . . .



depends upon its severity and the degree of disability it causes . . . A combination of aspirin, phenacetin and amphetamine [antispasmodic Benzedrine®], known under the . . . name of 'Edrisal', is useful . . ."

—Am. Pract. & Digest Treat.
8:1562 (October) 1957

Edrisal®

Antispasmodic Antidepressant Analgesic

2 TABLETS EVERY 3 HOURS

Smith Kline & French Laboratories, Philadelphia

Also available: 'Edrisal with Codeine' (¼ gr. & ½ gr.)

For full supplementation
of the essential nutritional factors in pregnancy—
FILIBON offers

- phosphorus-free formula
- new, well-tolerated source of iron, ferrous fumarate
- AUTRINIC* Intrinsic Factor Concentrate to augment the absorption of vitamin B_{12}
- prophylactic vitamins B_6 and K
- important trace elements

to keep her on the regimen you prescribe

- the FILIBON Jar, attractively designed for her
- the FILIBON Capsule, small, easy to swallow. Dry-filled for faster absorption, freedom from unpleasant aftertaste
- the FILIBON Dosage, convenient, only one a day

Each soft-shell FILIBON capsule contains:

Vitamin A	4,000 U.S.P. Units	Folic Acid	1 mg.
Vitamin D	400 U.S.P. Units	Ferrous Fumarate	90 mg.
Thiamine Mononitrate (B_1)	3 mg.	Iron (as Fumarate)	30 mg.
Pyridoxine (B_6)	1 mg.	Fluorine (CaF_2)	0.015 mg.
Niacinamide	10 mg.	Copper (CuO)	0.15 mg.
Riboflavin (B_2)	2 mg.	Iodine (KI)	0.01 mg.
Vitamin B_{12} with AUTRINIC Intrinsic Factor Concentrate	1/6 U.S.P. Oral Unit	Potassium (K_2SO_4)	0.835 mg.
		Manganese (MnO_2)	0.05 mg.
		Magnesium (MgO)	0.15 mg.
Ascorbic Acid (C)	50 mg.	Molybdenum ($Na_2MoO_4 . 2H_2O$)	0.025 mg.
Vitamin K (Menadione)	0.5 mg.	Zinc (ZnO)	0.085 mg.
		Calcium Carbonate	575 mg.

in the picture... during pregnancy

Filibon*

PHOSPHORUS-FREE PRENATAL VITAMIN MINERAL SUPPLEMENT **LEDERLE**

DOSAGE / one or more capsules daily
SUPPLIED / attractive re-usable bottles of 100 capsules

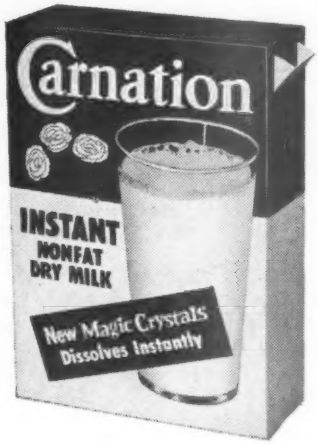
LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

*Reg. U. S. Pat. Off.

Carnation Instant nonfat dry milk

can be self-enriched for 25% more protein and better flavor than ordinary nonfat milk!

25% more nutrition and better flavor, too! The secret is the Carnation crystal form of nonfat milk—a form which adapts ideally to self-enrichment. The addition of one tablespoon of crystals per glass or ⅓ cup extra crystals per quart brings a new standard of fresh, delicious flavor to your patients, gives them an additional 25% nonfat milk nutrition with each serving. Result: "Difficult" patients respond to a richer and more palatable flavor, require 25% *less* fluid bulk to obtain the same amount of nutrition.



CONVENIENT: Carnation Instant "Magic Crystals" mix completely—even in ice-cold water—with just a slight stir. Always ready to drink immediately—in the office—at home or away from home.

DOCTOR—you, too, would enjoy the wholesome taste and the nourishing refreshment of this different and delicious nonfat milk discovery.

now...

to eliminate

severe

anorectal

inflammation...

start with steroid therapy

For severe anorectal inflammation Anusol is now also available as *Anusol-HC* ... hemorrhoidal suppositories with hydrocortisone.

Anusol-HC lets you *start* with steroid therapy . . . reduce and eliminate pain, heat, swelling, and hyperemia. With this simple two-stage program you can first check inflammatory symptoms safely, then *keep* patients comfortable:

1. ***Start** with 2 Anusol-HC Suppositories daily for 3 to 6 days.*
2. ***Maintain** with regular Anusol Suppositories or Unguent as required.*

Prescribe new Anusol-HC for safe and rapid control of harsh inflammation in hemorrhoids, proctitis and anal pruritus.

new Anusol®-HC

hemorrhoidal suppositories with hydrocortisone

WARNER-CHILCOTT
MORRIS PLAINS, N.J.

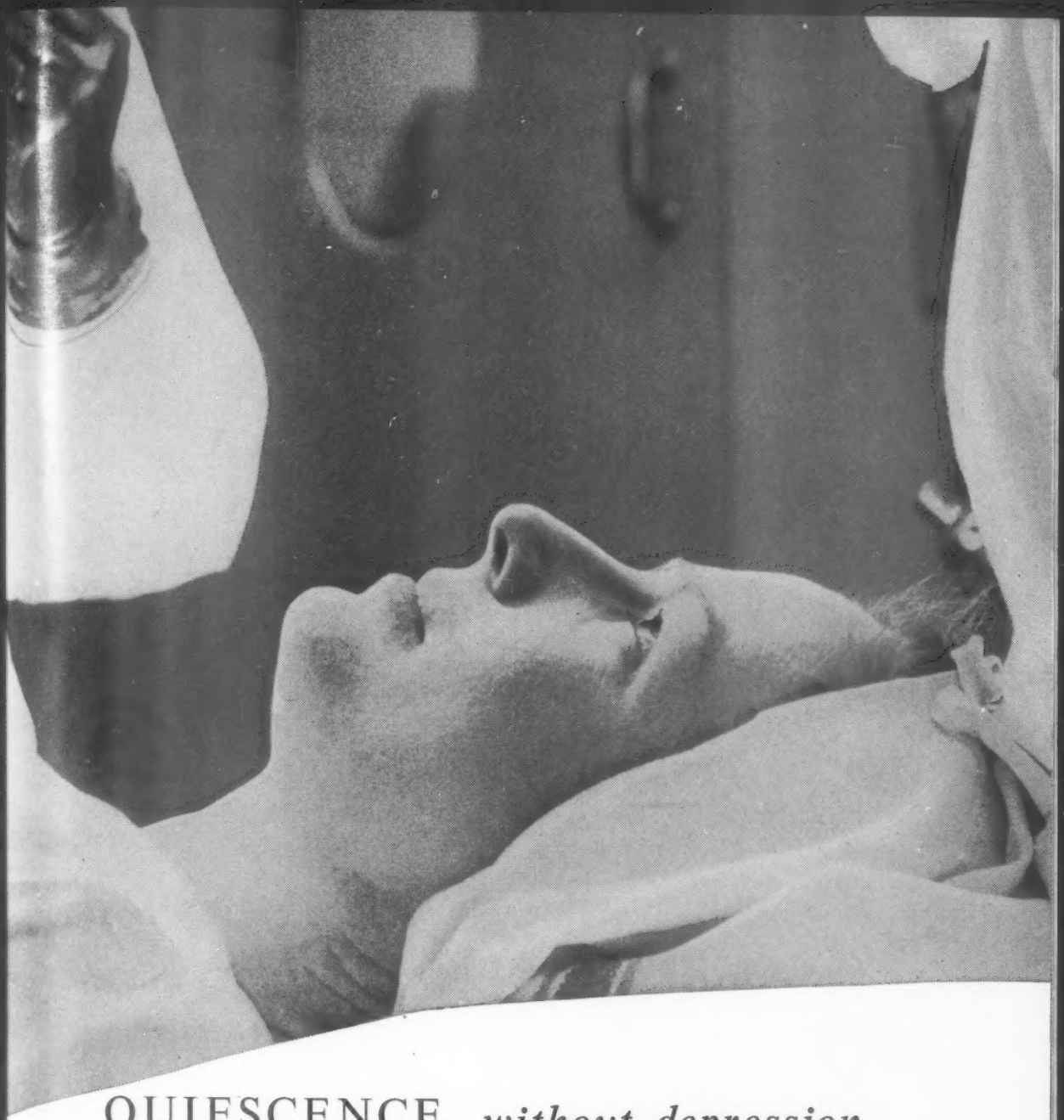
SOFTENS ACTIVATES

Metamucil® does BOTH!

In constipation, Metamucil produces SOFT, easy stools and activates gentle peristalsis. By adsorbing and retaining water within the stool Metamucil prevents hard feces from forming. And it adds to intestinal residue a soft, plastic bulk which ACTIVATES the normal reflex activity of peristalsis.

Metamucil is a brand of psyllium hydrophilic mucilloid with dextrose.

SEARLE



QUIESCENCE *without depression*

for surgical and obstetrical patients

PHENERGAN aids in carrying your patients through the difficult before-and-after periods of surgery and labor. It creates a state of quiescence without depressing vital functions. Light sleep is induced with easy awakening—providing better patient cooperation and management.

PHENERGAN, prophylactically and therapeutically, prevents postoperative excitement, nausea and vomiting—reduces analgesic, narcotic and sedative requirements.

PHENERGAN®

HYDROCHLORIDE

Promethazine Hydrochloride, Wyeth

INJECTION • TABLETS • SYRUP • SUPPOSITORIES

Comprehensive literature supplied on request

Wyeth®

Philadelphia 1, Pa.

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and hrou

NATABE

vitamin-mineral combination

KA

PARKE, DAVIS COMPAN

Detroit 32, Michigan

she needs support, too...

during pregnancy

and throughout lactation

BEC®

KAPSEALS®

Help protect her now, and you help insure better future health for her and her baby. A single NATABEC Kapseal each day provides all the vitamins and minerals the gravida or nursing mother needs to supplement a well-rounded diet.

each NATABEC Kapseal contains:

Calcium carbonate	600 mg.
Ferrous sulfate	150 mg.
Vitamin D	(10 mcg.) 400 units
Vitamin B_1 (thiamine) mononitrate	3 mg.
Vitamin B_2 (riboflavin)	2 mg.
Vitamin B_{12} (crystalline)	2 mcg.
Folic acid	1 mg.
Synkamin® (vitamin K) (as the hydrochloride)	0.5 mg.
Rutin	10 mg.
Nicotinamide (niacinamide)	10 mg.
Vitamin B_6 (pyridoxine hydrochloride)	3 mg.
Vitamin C (ascorbic acid)	50 mg.
Vitamin A	(1.2 mg.) 4,000 units
Intrinsic factor concentrate	5 mg.

dosage As a supplement during pregnancy and throughout lactation, one or more Kapseals daily. Available in bottles of 100 and 1,000.

36558

uterotubal X-rays with

far more contrast—for definitive diagnosis
far less pain—for the apprehensive patient

ETHIODOL®

(Brand of Ethiodized Oil)

advantages clinically confirmed[1,2]

- far more contrast and clarity than with aqueous media[1,2]
- free-flowing viscosity—fluidity similar to distilled water[1]
- absence of notable pain[1,2]
- permits 24-hour film for more accurate study of tubal patency[1,2]
- optimal absorption characteristics[1]
- more information than Rubin test for sterility diagnosis[1,2]

ETHIODOL,® brand of ethiodized oil, is the ethyl ester of the iodized fatty acids of poppy seed oil, containing 37% iodine. It is available in 10-cc. ampules, boxes of two. A development of Guerbet Laboratories.

sources: (1) Steinberg, W.: Am. J. Obst. & Gynec. 75:144, 1958.
(2) Becker, S.: J. Am. M. Women's A. 12:332, 1957.

FOUGERA E. FOUGERA & COMPANY, INC • Hicksville, Long Island, New York

"...following effective treatment, there is a dramatic improvement in the subjective symptoms of iron deficiency long before the anemia is corrected."*

"There was...[with IMFERON]...a reduction in blood transfusions of from 50 pints for every 100 deliveries to 14.5 pints for every 100 deliveries...[and then]...to only 7 pints for every 100 deliveries."*

*from the new
color and sound
Medical Motion Picture

INTRAMUSCULAR IRON THERAPY

filmed in England and the United States

loaned without charge to state and county medical societies, medical schools, and interested medical groups.

write to:

MEDICAL EDUCATION DEPARTMENT
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Imferon®

INTRAMUSCULAR IRON-DEXTRAN COMPLEX

"...well-tolerated and effective."†
†Bethell, F. H.: GP 18:97 (July) 1958.

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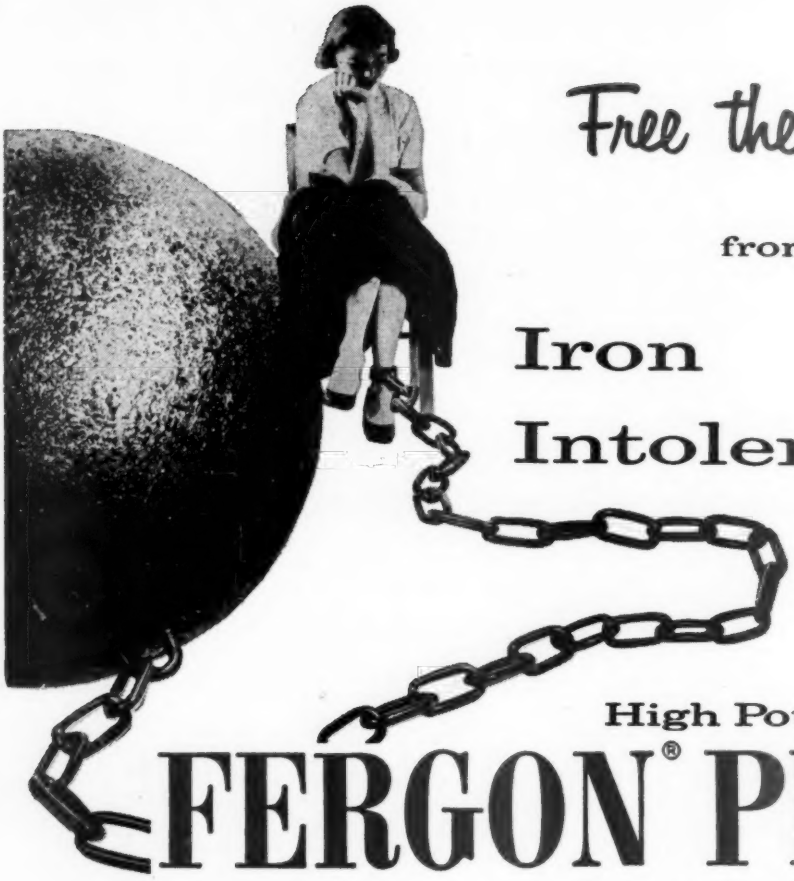


Free the anemic

from

Iron Intolerance

High Potency

FERGON® PLUS

Improved Caplets®

2 Caplets = 1 U.S.P. oral unit of Anti-Anemia Activity *without* gastrointestinal upset

2 Caplets contain:

Fergon (brand of ferrous gluconate) Iron without Irritation	1000 mg.
Vitamin B_{12} with Intrinsic Factor Concentrate U.S.P.	1 unit (oral)
Folic acid	3 mg.
Ascorbic acid	150 mg.

Highest Hemoglobin Response

No Nausea
No Abdominal Cramps
No Constipation
No Diarrhea
in approximately 90% of patients

Therapeutic dose: Only 2 Fergon Plus Caplets daily (one before the morning and evening meals).

How Supplied:

Fergon Plus Improved Caplets, bottles of 100 and 500 easy to swallow Caplets.

Winthrop LABORATORIES NEW YORK 18, N. Y.

Fergon (brand of ferrous gluconate) and Caplets, trademarks reg. U. S. Pat. Off.

Assuredly

the lady is fastidious

Massengill® powder

when recommending a vaginal douche

Massengill Powder has a "clean" antiseptic fragrance. It enjoys unusual patient acceptance.

Massengill Powder is buffered to *maintain* an acid condition in the vaginal mucosa. It is more effective than vinegar and simple acid douches.

Massengill Powder has a low surface tension which enables it to penetrate into and cleanse the folds of the vaginal mucosa.

Massengill Powder solutions are easy to prepare. They are nonstaining, mildly astringent.

Indications: Massengill Powder solutions are a valuable adjunct in the management of monilia, trichomonas, staphylococcus, and streptococcus infections of the vaginal tract. Regular douching with Massengill Powder solution minimizes subjective discomfort and maintains a state of cleanliness and normal acidity without interfering with specific treatment.

Currently, mailings will be forwarded only at your request. Write for samples and literature.

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE • NEW YORK • SAN FRANCISCO • KANSAS CITY

In modern feminine hygiene and therapy

massengill® powder

Massengill Powder has cosmetic elegance. Its clean, refreshing fragrance is acceptable to the most fastidious for therapeutic or routine hygienic use. Massengill Powder solutions are easily prepared, convenient to use, nonstaining. They effectively cleanse, deodorize and soothe the vaginal mucosa, while their mild astringent properties tend to decrease vaginal secretions.

CLEAN-UP AFTER ANTIBIOTICS

Following intensive antibiotic therapy, increasing numbers of female patients return complaining of vulvar pruritus or vaginitis . . . and profuse vaginal discharge.

Most of these present the classical picture of Monilia albicans, Trichomonas vaginalis or mixed infections. When these infections occur, regular use of Massengill Powder, with its pH of 3.5 to 4.5, helps restore the normal acidity of the vaginal tract. At this normal pH the growth of pathogenic organisms is inhibited and the growth of the normal vaginal flora encouraged,[1] thus reducing the barriers to specific medication.

LOW pH RETENTION

Massengill Powder is buffered to retain an acid condition. In a recent clinical observation, ambulatory patients—with an alkaline vaginal mucosa resulting from pathogens—maintained an acid vaginal mucosa of pH 3.5 for a period of 4 to 6 hours after douching with Massengill Powder; recumbent patients maintained a satisfactory acid condition up to 24 hours. Simple acid douches (vinegar or lactic acid) are quickly neutralized by an alkaline vaginal mucosa; therefore, they are somewhat unsatisfactory in maintaining the required acid pH of the vagina.[2]

LOWER SURFACE TENSION

Massengill Powder in the standard solution has a surface tension of 50 dynes/cm. as compared to that of water and simple acid solutions with 72 dynes/cm. This added property of reduced surface tension enables Massengill Powder to penetrate into and cleanse the folds of the vaginal mucosa, thus increasing the therapeutic effectiveness. Lowered surface tension makes the cell wall and cytoplasmic membrane of the infecting organism more permeable and thus more susceptible to specific therapy.[2]

SUPPLY

Massengill Powder is supplied in glass jars of the following sizes:

Small, 3 oz.
Medium, 6 oz.
Large, 16 oz.
Hospital Size, 5 lbs.

Pads of douching instructions for patient use available on request.

REFERENCES

1. Lang, W.R., Rakoff, A.E., Am. Geriatrics Soc. *1*:520 (1953).
2. Arnot, P.H., The Problem of Douching, Western Journal of Surg., Obs., and Gyn., Vol. 62, No. 2:85 (1954).

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE • NEW YORK • SAN FRANCISCO • KANSAS CITY

THORAZINE*

"standard" medication for patients in labor[1]

'Thorazine' was used during labor in a series of 2,093 obstetrical patients in an effort to achieve relief of pain and adequate sedation of the mother without causing respiratory depression in the infant.

Relief of pain was good in the great majority of patients. Also, apprehension, nausea and vomiting were markedly reduced. Condition of infants at birth was good; only 2.6% required active resuscitation.

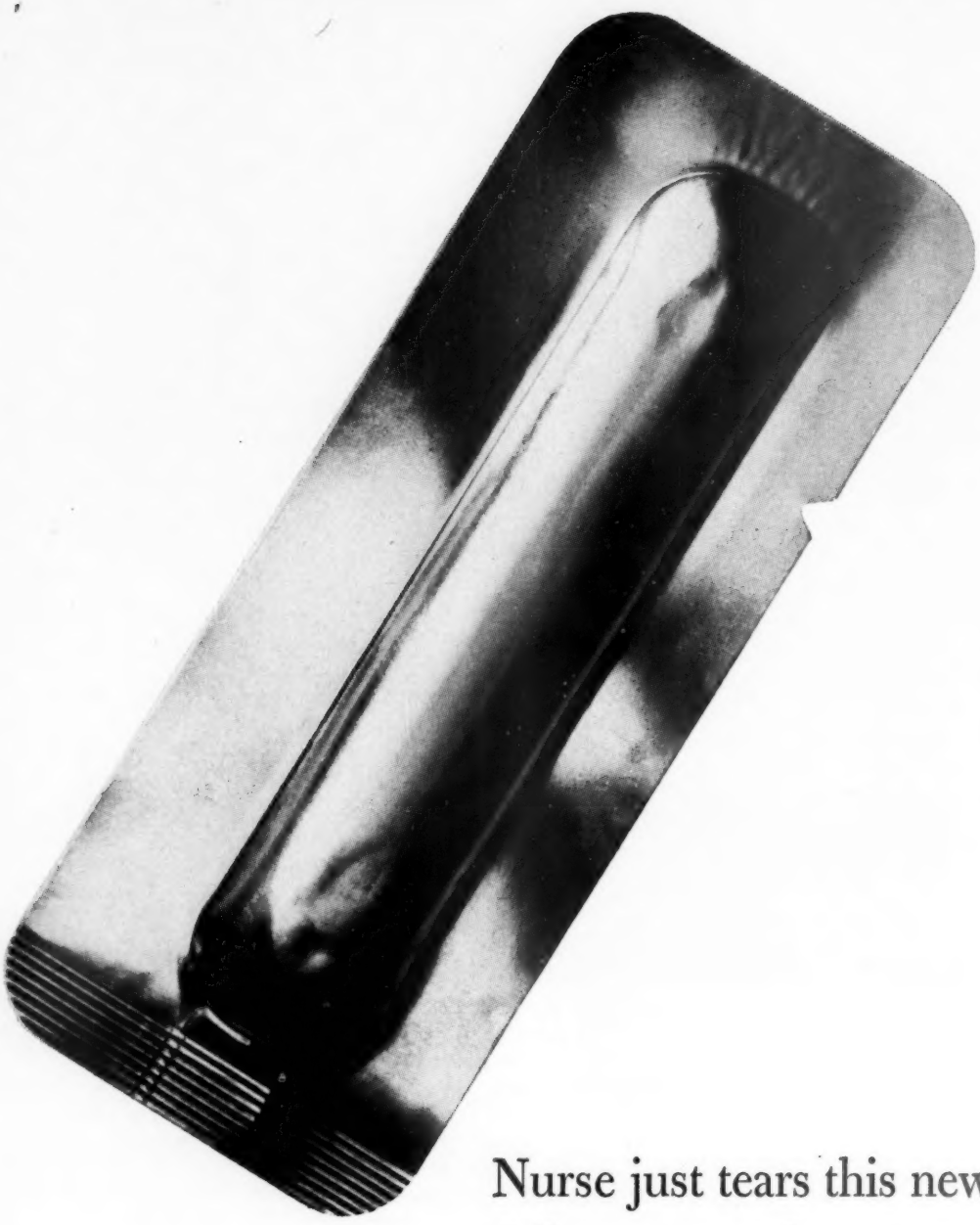
Only six patients showed significant hypotension even though 1,030 received saddle-block anesthesia.

The authors state that the good results obtained over a two-year period have made 'Thorazine' a standard drug for patients in labor.

1. Lindley, J.E.; Rogers, S.F., and Moyer, J.H.: Obst. & Gynec. *10*:582 (Nov.) 1957.

Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.



Nurse just tears this new
foil suture packet open
to give you stronger,
more pliable surgical gut.
It's sterilized by electron beam.

ETHICON®

For the menopause

two potencies of Milprem

Milprem®-400

400 mg. MILTOWN® + 0.4 mg. CONJUGATED ESTROGENS (equine)

new Milprem®-200

200 mg. MILTOWN® + 0.4 mg. CONJUGATED ESTROGENS (equine)

Miltown acts immediately to

- *relieve emotional symptoms*
- *relax skeletal muscle; relieve tension headache and low back pain*

Conjugated estrogens (equine)

- *help restore endocrine balance*
- *relieve vasomotor and metabolic disturbances*

SUPPLIED: Bottles of 60 tablets.

DOSAGE: 1 tablet t.i.d. in 21-day courses with one week rest periods. Should be adjusted to individual requirements.

Literature and samples on request.

WALLACE LABORATORIES, *New Brunswick, N. J.*

CMP-8170-128

THE *Doyle* PELVISCOPE*

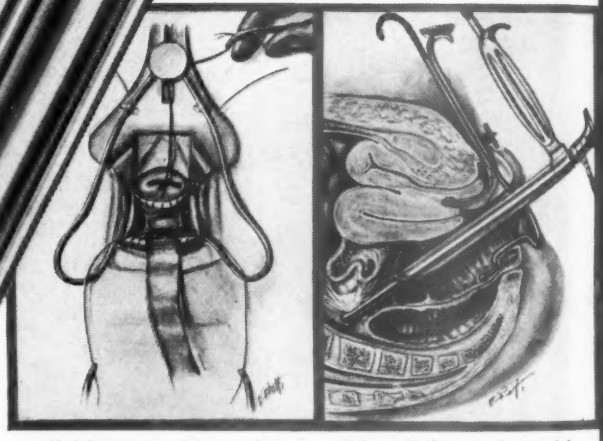
for use in culdotomy as an aid to early diagnosis and relief of pelvic disorders

The Doyle Pelviscope provides a means for magnified visualization of the pelvic regions through a culdotomy opening. Diagnostic indications for the procedure are

early detection of
tubal pregnancy
endometriosis
ovarian or pelvic cancer

and differentiation of
pelvic organic disease
from psychoneurosis

The Pelviscope (Cat. No. 5200) consists of cannula, telescope retractor with twin light carriers and handle to position telescopes, right angle telescope, foroblique telescope with standard accessories in case.



Culdotomy orifice, with continuous suturing of vagina to peritoneum.

The pelviscope in position, showing an elongated tortuous tube at ovulation.

""Use of the Pelviscope in Culdotomy", J. A. M. A., Feb. 21, 1953, Vol. 151, No. 8.*

ESTABLISHED IN 1900 BY REINHOLD WAPPLER

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

8 PELHAM PARKWAY PELHAM MANOR, N. Y.

two NEW prenatal supplements / *both especially for multiparas –*

(3 out of 4 prenatal patients[2])

new

Per cent anemic[1]

Natalins® Comprehensive

Vitamins and minerals, Mead Johnson

tablets

12 significant vitamins and minerals

Natalins® Basic

Vitamins and minerals, Mead Johnson

tablets

4 basic vitamins and minerals

convenient one-a-day dosage

two formulations to meet individual needs of your patients

- **the need of the multipara for supplemental nutrition may be greater . . .**

  as successive pregnancies deplete her stores of nutrients—

  Anemia has been found to occur more frequently in multiparas than in primigravidas[1]—

  Natalins Comprehensive and Basic meet this need generously—iron (40 mg. per tablet), ascorbic acid (100 mg. per tablet) and calcium (250 mg. per tablet).

76% of births in 1958 will be to multiparas[2] . . . Probably 3 out of 4 of your pregnant patients have borne children previously.

Mead Johnson

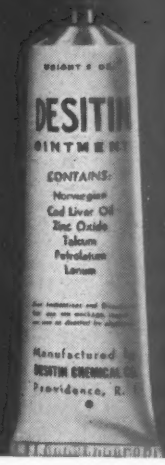
Symbol of service in medicine

MA707

1. Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.
2. Projected estimate based on data from U. S. Office of Vital Statistics 1951-1965.

studies in 706 patients
show that

DESITIN®
OINTMENT



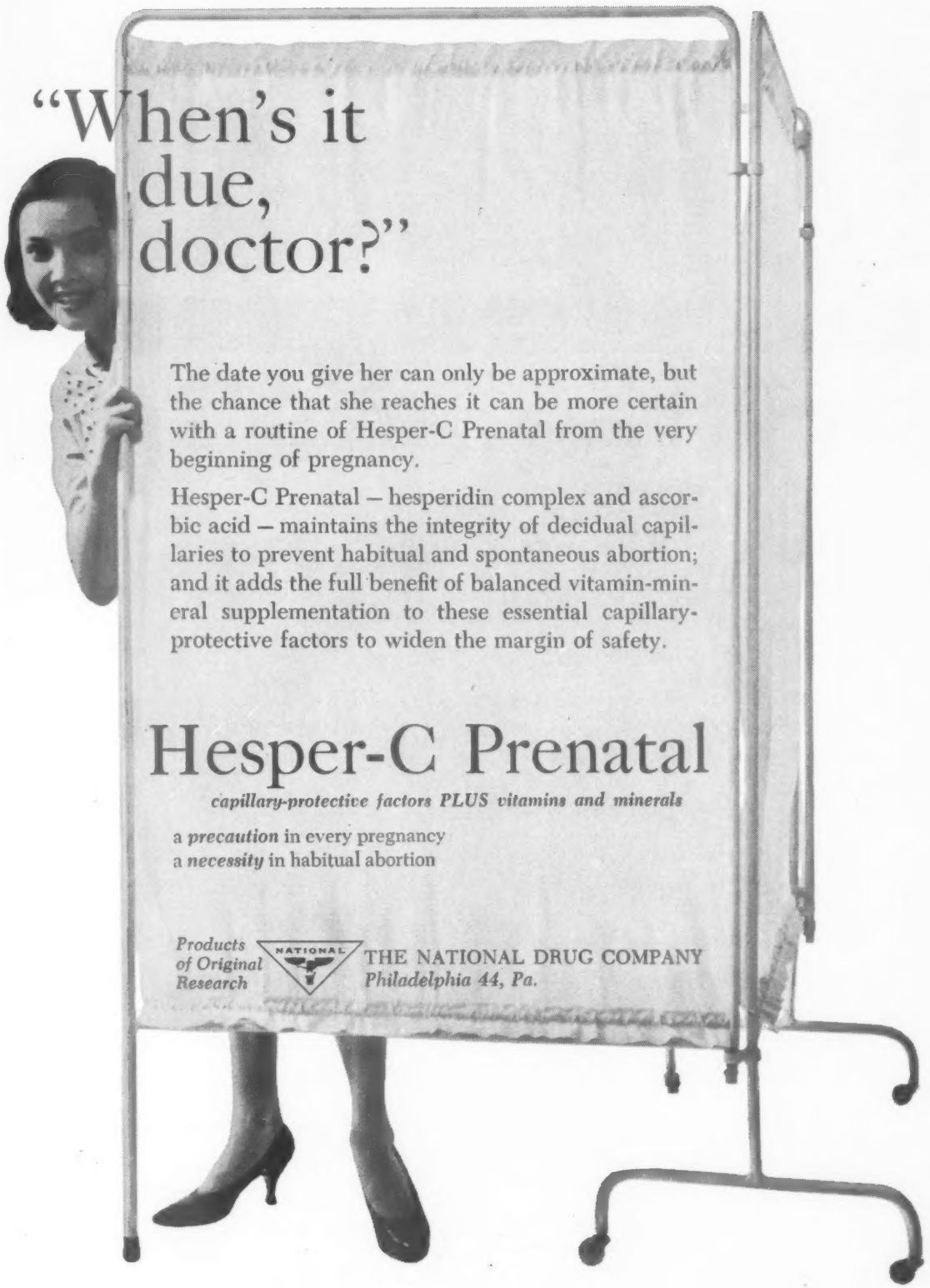
promotes
"early, clean and healthy healing"[1]

in
- traumatic and infectious wounds
- burns (first, second, third degree)
- abdominal fistulae and wounds
- pressure sores and ulcers
- pilonidal cysts and sinuses
- ano-rectal wounds • chest wounds

samples and new reprint[1] on request.

DESITIN CHEMICAL COMPANY
812 Branch Ave., Providence 4, R. I.

1. Grayzel, H. G., and Schapiro, S.: Western J. Surgery, Obstet. & Gyn., Oct. 1956.



"When's it due, doctor?"

The date you give her can only be approximate, but the chance that she reaches it can be more certain with a routine of Hesper-C Prenatal from the very beginning of pregnancy.

Hesper-C Prenatal – hesperidin complex and ascorbic acid – maintains the integrity of decidual capillaries to prevent habitual and spontaneous abortion; and it adds the full benefit of balanced vitamin-mineral supplementation to these essential capillary-protective factors to widen the margin of safety.

Hesper-C Prenatal

capillary-protective factors PLUS vitamins and minerals

a ***precaution*** in every pregnancy
a ***necessity*** in habitual abortion

Products of Original Research

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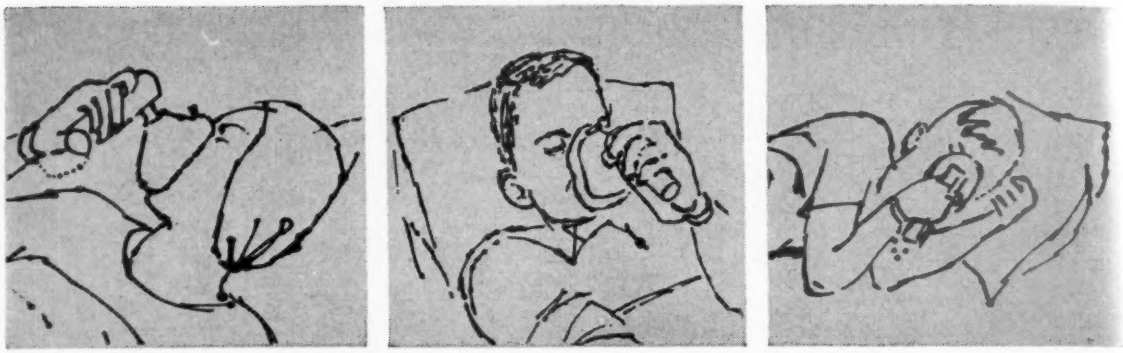
THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

MCP 1808/59

FOR SELF-ADMINISTERED INHALATION ANALGESIA



IN OBSTETRICS IN MINOR SURGERY IN PEDIATRICS

"Trilene"® *and the*

Brand of trichloroethylene U.S.P. (Blue)

"Duke"® University Inhaler

No. 3160 Model-M

- *notably safe and effective*

"Trilene," self administered with the "Duke" University Inhaler, under proper medical supervision, provides highly effective analgesia with a relatively wide margin of safety.

- *convenient to use*

The "Duke" University Inhaler (Model-M) is specially designed for economy, facility of handling, and ready control of vapor concentration.

- *special advantages*

Induction of analgesia is usually smooth and rapid with minimum or no loss of consciousness. Patients treated on an ambulatory basis can usually leave the doctor's office or hospital within 15 to 20 minutes. Inhalation is automatically interrupted if unconsciousness occurs.

"Trilene" *alone* is not recommended for anesthesia nor for the induction of anesthesia. Epinephrine is contraindicated when "Trilene" is administered.

"Trilene" is available in 300 cc. containers.

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

Ayerst

Ayerst Laboratories make "Trilene" available in the United States by arrangement with Imperial Chemical Industries Limited.

5718

AFTER THE BLESSED EVENT

DERMOPLAST®

AEROSOL SPRAY

SOOTHING TOPICAL ANESTHETIC • BACTERICIDAL • FUNGICIDAL

APPLIED WITHOUT TOUCHING THE INVOLVED SENSITIVE AREAS—*Immediate relief of pain and itching is experienced*

Formula: benzocaine 4.7% benzethonium chloride 0.1%; menthol 0.5%; dissolved in oils (DOHO PROCESS)

Available in 3 sizes:

PRESCRIPTION: new 3 oz. (for individual therapy in hospital & home)

HOSPITAL: 12 oz. economy

JUNIOR: 6 oz.

Other indications responding to DERMOPLAST's quick, therapeutic pain relief:

perineal suturing
hemorrhoids
pruritus vulvae
wounds
burns
abrasions
sunburn

Supporting clinical data on request

MALLON DIVISION OF DOHO

100 VARICK ST., NEW YORK 13, N. Y.

AVOIDS UTERINE HEMORRHAGE

Vallestril®

AMELIORATES MENOPAUSAL SYMPTOMS IN A HIGH PERCENTAGE OF PATIENTS

Vallestril (brand of methallenestril) has a unique pharmacologic advantage in that its low-dosage effectiveness in controlling menopausal symptoms is rarely accompanied by withdrawal bleeding.

Schneeberg, Perczek, Nodine and Perloff* gave Vallestril to fifty-two menopausal patients and compared it with several other estrogenic compounds. They reported: "[Vallestril] was found to be a satisfactory therapeutic agent in menopausal syndrome in 50 of 52 patients (96 per cent). . . . Vaginal bleeding during therapy or upon withdrawal of therapy was infrequent and generally observed only when larger than therapeutic doses were prescribed. . . . [Vallestril] compares favorably with other estrogenic compounds in all respects, and was, in many instances, found to be the more satisfactory upon direct comparison in the same patient."

For the menopausal syndrome the investigators used 10 mg. of Vallestril daily until symptoms were controlled and then 5 mg. for two weeks with gradual tapering off. Medication should be interrupted every four months to determine the need for further therapy. G. D. Searle & Co., Chicago 80, Illinois. Research in the Service of Medicine.

*Schneeberg, N. G.; Perczek, L.; Nodine, J. H., and Perloff, W. H.: Methallenestril, a New Synthetic Estrogen, J.A.M.A.*161*:1062 (July 14) 1956.

SEARLE

In trichomoniasis, moniliasis, nonspecific vaginitis

BETADINE® kills outright

Brand of Povidone-Iodine

Kills by contact . . . virtually nonirritating to vaginal mucosa . . . is effective even in presence of blood, pus or vaginal secretions . . . will not permanently stain linen or clothing: color can be washed off with water.

Regimen: In the office—swab with Betadine Antiseptic, full strength.

For patients' use at home—Betadine Vaginal Douche between office visits.

Available: Betadine Antiseptic in 8-oz. and 16-oz. bottles. Betadine Vaginal Douche in 8-oz. bottles.

Write for literature and samples Department "A"

virtually nonirritating to vaginal mucosa

TAILBY-NASON COMPANY, INC.
DOVER, DELAWARE

to relieve edema of

DIURIL® "

CHLOROTHIAZIDE

FINNERTY, F. A., Buchholz, J. H. and Tuckman, J.: J.A.M.A. **166**:141, Jan. 11, 1958.

DIURIL (Chlorothiazide) given alone to 85 patients, ". . . caused an excellent diuresis, with reduction of edema, weight, blood pressure, and albuminuria. . . . The average effective dose was found to be 1 Gm. per day by mouth. . . . The usually excellent response coupled with the absence of significant toxicity and lack of development of drug resistance makes chlorothiazide ideal for the prevention and treatment of toxemia."

DOSAGE: one or two 500 mg. tablets of DIURIL once or twice a day.

SUPPLIED: 250 mg. and 500 mg. scored tablets DIURIL (chlorothiazide); bottles of 100 and 1,000.

DIURIL is a trademark of Merck & Co., Inc.

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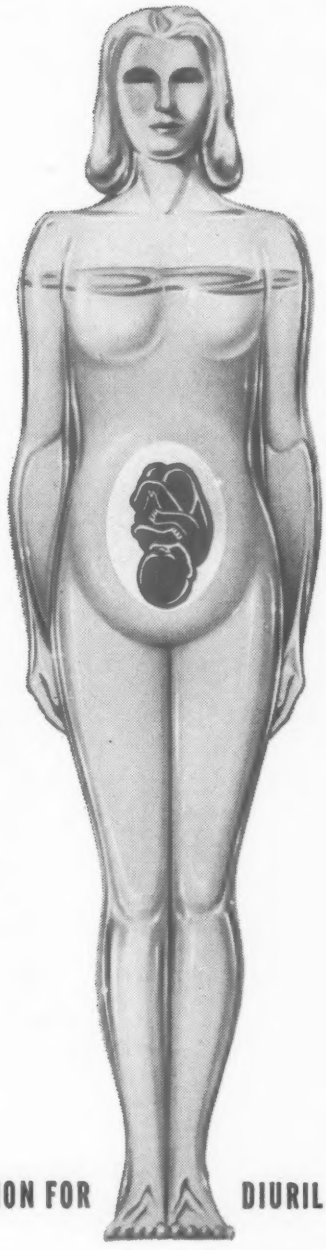
MERCK SHARP & DOHME Division of MERCK & CO., INC., Philadelphia 1, Pa.

pregnancy

.....caused an excellent diuresis, with reduction of edema, weight, blood pressure, and albuminuria...."



ANY INDICATION FOR DIURESIS IS AN INDICATION FOR DIURIL

Not available to the wives
of Henry VIII despite
the wealth of his realm
A NEW ACHIEVEMENT

Now available at low cost to all your patients during pregnancy & lactation New MOL-IRON® PRENATAL

wide-range Nutritional supplement/phosphorus-free

NEW ECONOMY: less than ½ the usual cost.

NEW CONVENIENCE: only 1 tablet a day.

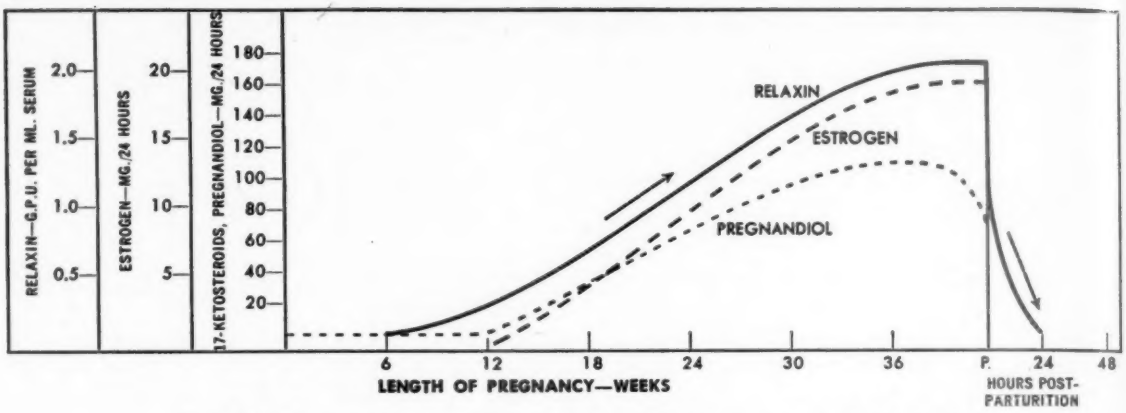
Especially "special" because of MOL-IRON, the unique molybdenized ferrous iron complex–for over 10 years unexcelled in tolerance and effectiveness, particularly in pregnant women!

Bottles of 30 (month's supply)/Bottles of 90 (trimester's supply)

White's WHITE LABORATORIES, INC., Kenilworth, New Jersey

Just one Tablet a day provides:	
Vitamin A	6000 U.S.P.U.
Vitamin D	600 U.S.P.U.
Vitamin K	2 mg.
Vitamin E	1 Int.U.
Vitamin C (Ascorbic Acid)	100 mg.
Thiamine	5 mg.
Vitamin B_{12}	2 mcg.
Folic Acid	0.25 mg.
Riboflavin	5 mg.
Pyridoxine	2 mg.
Panthenol	5 mg.
Nicotinamide	30 mg.
Mol-Iron:	
Ferrous Sulfate	75 mg.
Molybdenum Oxide	1.1 mg.
Calcium	150 mg.
Cobalt	0.1 mg.
Copper	1 mg.
Iodine	0.2 mg.
Magnesium	6 mg.
Manganese	1 mg.
Potassium	5 mg.
Zinc	1.5 mg.

Relaxin: an essential hormone of parturition



to reinforce the normal physiology of childbirth

Cervilaxin

(relaxin, National)

for shorter labor, easier delivery

Clinical studies of relaxin as a cervical relaxant in 564 parturient women—

Israel[1]	20 patients	"preliminary clinical impression is highly favorable"
Eichner[2]	32 patients	"definite softening . . ."
Hodgkinson[3]	20 patients	"impressed with the soft state of the cervix."
Eisenberg[4]	117 patients	"rapid softening and dilatability"
Pou de Santiago[5]	20 patients	"dilatation not only at the cervix but also in the perineum"
Birnberg[6]	258 patients	"Cervilaxin alone produces a marked softening of the cervix"
Stone[7]	97 patients	"relaxin does soften the cervix"
Total:	564 patients	

In spontaneous or induced labor at term, *Cervilaxin*—the third ovarian hormone—aids the normal physiology of parturition, softening and relaxing the cervix, safely, without side effects, to help

1. **shorten labor**
2. **reduce fetal damage and maternal complications**
3. **make the use of oxytocin safer**

Cervilaxin should be administered by intravenous drip, and is supplied in 2-ml. vials containing 20 mg./ml., with detailed instructions in each package.

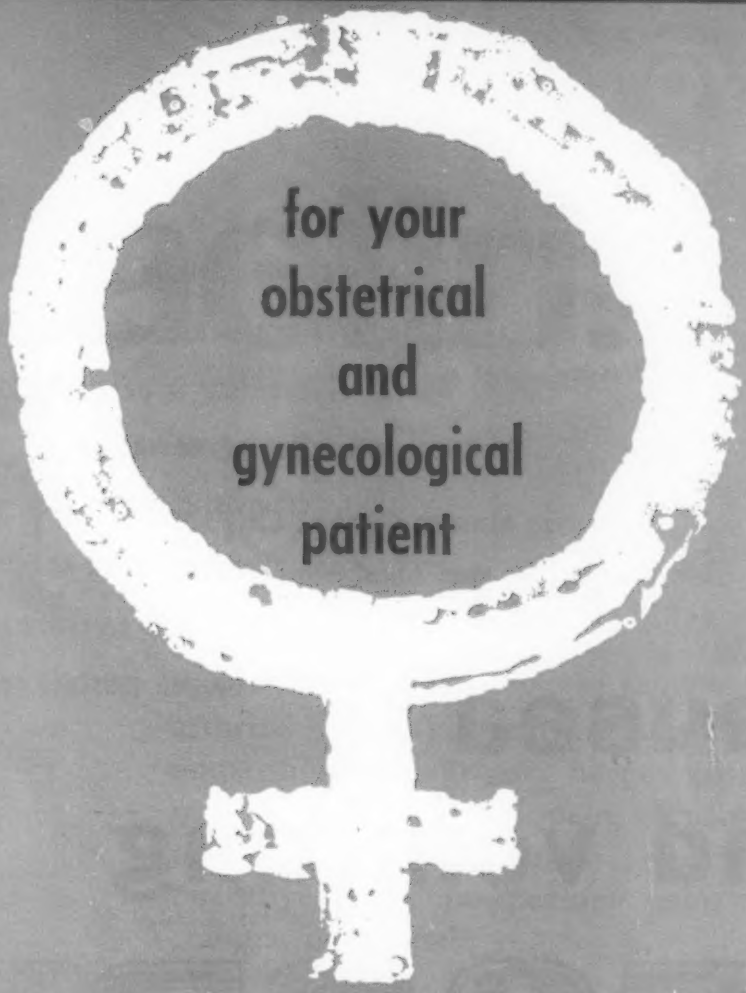
References: 1. Israel, S.L.: Personal Communication. 2. Eichner, E., *et al.*: Am. J. Obst. & Gynec. *71*:1035, 1956. 3. Hodgkinson, C.P.: Am. J. Obst. & Gynec. *71*:1035, 1956. 4. Eisenberg, L.: J.A.O.A. *57*:146, 1957. 5. Pou de Santiago, A.: Peruvian Obst. & Gynec. Soc., 2nd Uruguayan Conference on Obst. & Gynec., 1957. 6. Birnberg, C.H., and Abitbol, M.M.: Obst. & Gynec. *10*:366, 1957. 7. Stone, M.L.: Effects of Relaxin on Term and Premature Labor, Conf. on The Uterus, The New York Academy of Sciences, Feb. 12-15, 1958.

Products of Original Research

NATIONAL

THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

CE-921/58



BACULIN
VAGINAL TABLETS

FUNGICIDAL . . . BACTERICIDAL . . . PROTOZOICIDAL COMPREHENSIVE TREATMENT OF VAGINAL INFESTATION.

A single **BACULIN** *vaginal tablet generally destroys the causes o vaginitis, namely Trichomonas Vaginalis, Candida Albicans, and non-specific organisms. Prescribe* **BACULIN** *vaginal tablets in your next case of non-venereal vaginitis.*

desplex
ANTIABORTIVE

ACCIDENTS OF PREGNANCY CAN NOT BE CURED. THEY MUST BE PREVENTED
desplex IS A CLINICALLY PROVED ANTIABORTIVE.

des*plex, a unique combination of ultramicronized diethylstilbestrol and vitamins C, and B complex, was shown 96% effectiv in carrying 1200 difficult pregnancies to term.*[1] *For assurance of a successful pregnancy, prescribe* **des***plex tablets. Now contains hesperidin complex.*

BANAUSEA
TABLETS

ANTINAUSEANT, ANTIEMETIC — BAN NAUSEA AND VOMITING OF PREGNANCY . . . SAFELY . . . EFFECTIVELY . . . ECONOMICALLY.

Just prescribe **BANAUSEA** *tablets, one upon arising and one at bedtime. Turn your patients' blue mornings pink with* **BANAUSEA** *tablets.*

Samples upon request.

Reference: 1. Peña, E. F., Med. Times, 82-921, 1954.

A&G Amfre-Grant, Inc., Brooklyn 26, N. Y.

- postoperatively
- in pregnancy when vomiting is persistent
- following neurosurgical diagnostic procedures
- in infections, intra-abdominal disease, and carcinomatosis
- after nitrogen mustard therapy

for nausea and vomiting

VESPRIN

Squibb Trifluprom azine

- provides prompt, potent, and long-lasting control
- capable of depressing the gag reflex
- effective in cases refractory to other potent antiemetic agents
- may be given intravenously, intramuscularly and orally
- no pain or irritation on injection

ANTIEMETIC DOSAGE:
Intravenous: 8 mg. average single dose
Dosage range 2-10 mg.
Intramuscular: 15 mg. average single dose
Dosage range 5-15 mg.
If subsequent parenteral dose is needed, one-half the original dose will usually suffice
Oral: 10-20 mg. initially; then 10 mg. t.i.d.

SUPPLY:
Parenteral solution – 1 cc. ampuls (20mg./cc.)
Oral tablets – 10 mg., 25 mg., 50 mg., in bottles of 50 and 500

SQUIBB *Squibb Quality – The Priceless Ingredient*

"VESPRIN" ® IS A SQUIBB TRADEMARK

PAIN Zactirin®

Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth

for everyday pain control . . .

for your many patients requiring potent analgesia but not an injected narcotic

Proved by extensive evaluation[1,2,3] in 1998 patients in diverse areas of medicine and surgery, including:

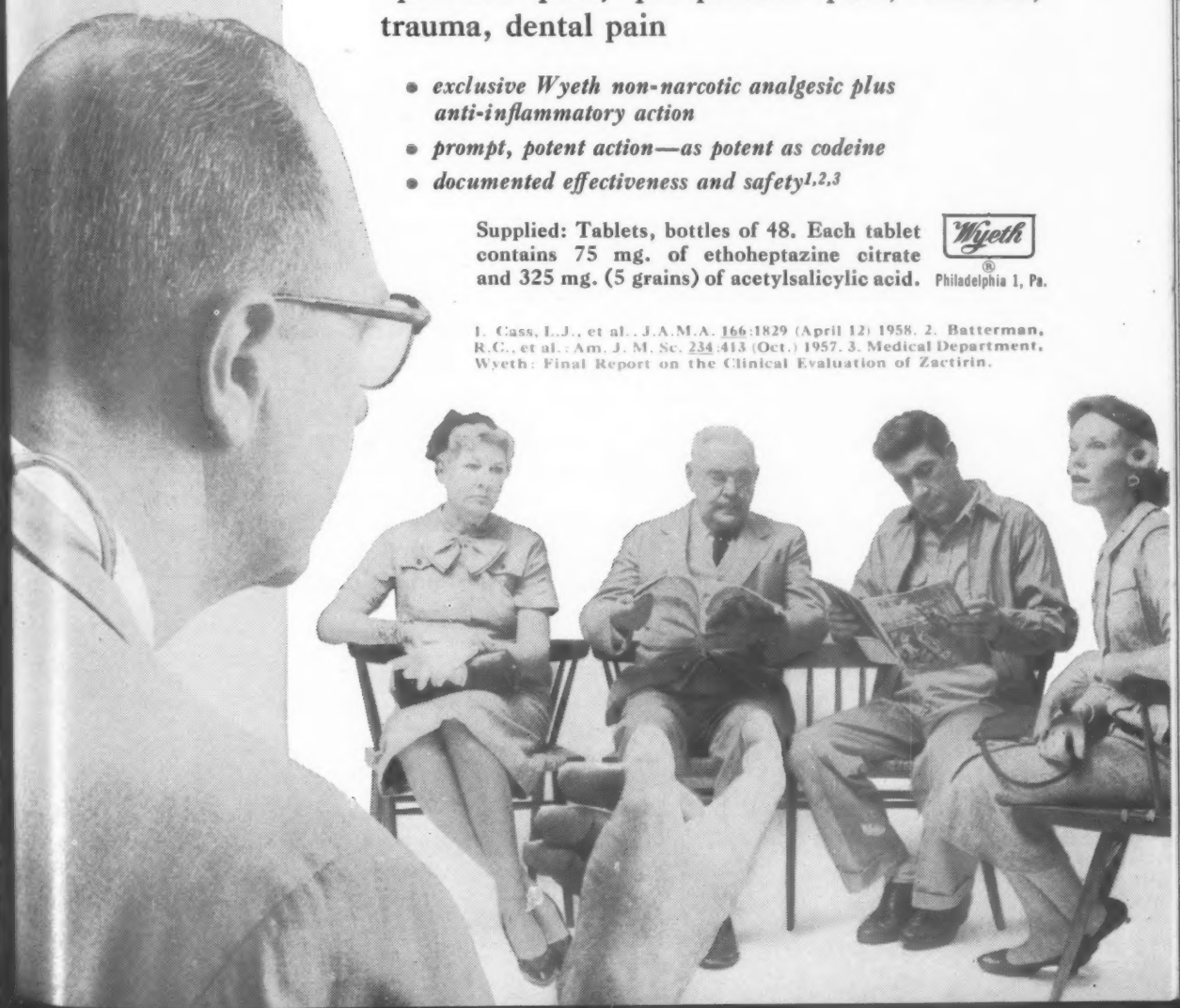
arthritis, bursitis, early metastatic carcinoma, fibrositis, grippe, herpes zoster, ligamental strain, low back pain, menstrual pain, myalgia, myositis, neuritis, pleurisy, postoperative pain, postpartum pain, sciatica, trauma, dental pain

- *exclusive Wyeth non-narcotic analgesic plus anti-inflammatory action*
- *prompt, potent action—as potent as codeine*
- *documented effectiveness and safety[1,2,3]*

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

Wyeth®
Philadelphia 1, Pa.

1. Cass, L.J., et al.: J.A.M.A. 166:1829 (April 12) 1958. 2. Batterman, R.C., et al.: Am. J. M. Sc. 234:413 (Oct.) 1957. 3. Medical Department, Wyeth: Final Report on the Clinical Evaluation of Zactirin.



Meat...

and its fat-protein calorie ratio*

For every calorie of fat provided by the average American dietary only 0.3 calorie of protein is provided. The quality of this protein ranges from poor to excellent.

On the other hand, cooked meat as usually eaten supplies from three to five times this number of protein calories in relation to the calories derived from its fat. The protein of meat is invariably of high biologic quality.

	Calories from Fat	Calories from Protein
in the average American dietary	1	0.3
in beef rump roast	1	1.27
in beef flank steak	1	1.42
in lamb leg roast	1	1.55
in pork loin chop (lean portion only)	1	1.36
in cured ham	1	1.04
in veal cutlet (lean portion only)	1	1.40

The high protein yield of meat exceeds that from any other main dish food in man's diet. The amino acid composition of meat protein closely approaches the quantitative proportions needed for effective biosynthesis of human tissue.

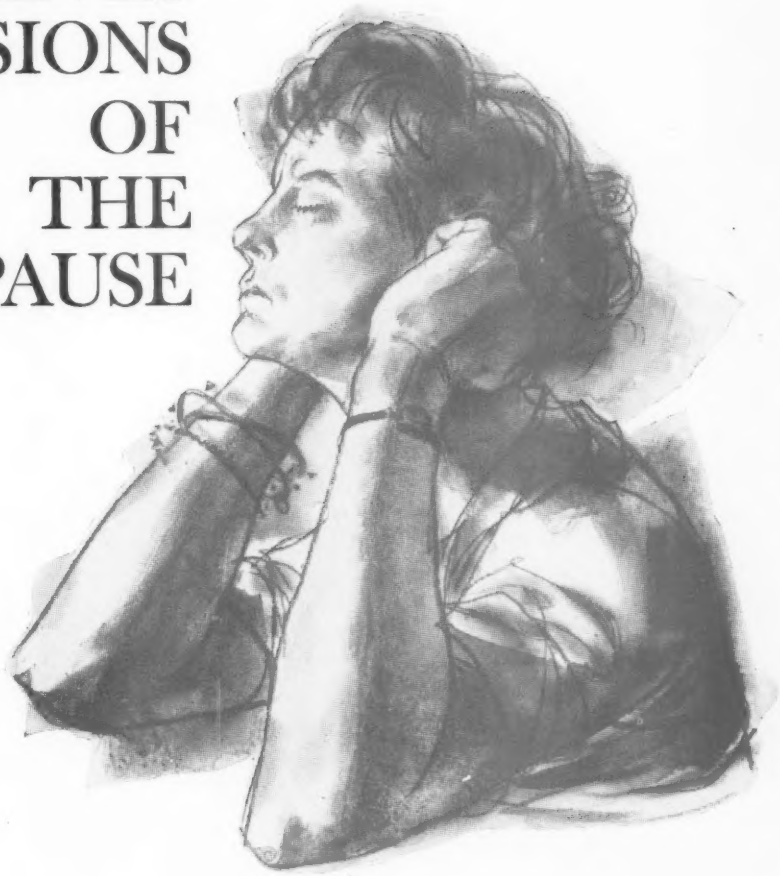
Meat—the chief source of top-quality protein, B vitamins, and minerals in the American diet—is also an excellent vehicle for nutritionally valuable fat, the amount of which is readily controlled by trimming and by selection of cuts.

*Leverton, R.: The Fat, Protein, and Calorie Value of Cooked Meats. Proc. 9th Research Conf. sponsored by the Council on Research of the American Meat Institute, University of Chicago, March 1957.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago...Members Throughout the United States

RELIEVES TENSIONS OF THE MENOPAUSE



IN THE MENOPAUSE, "the most trying symptoms come as a result of tension and fear and are manifested by weakness . . . exhaustion, insomnia . . ."[1]

- Miltown facilitates emotional adjustment to the menopause
- promptly relieves tension, irritability
- relaxes skeletal muscle, relieves tension headache and low back pain
- promotes restful sleep without depressive hang-over
- does not interfere with mental or physical faculties
- does not affect autonomic function

CM-8130

Miltown®

meprobamate (Wallace)

Available in 400 mg. scored and 200 mg. sugar-coated tablets.

Also available as MEPROSPAN* (200 mg. meprobamate *continuous release* capsules).

In combination with conjugated estrogens (equine): MILPREM®-400 and MILPREM®-200.

1. Farquharson, R. F.: The menopausal patient. M. Rec. & Ann. 49:196, Feb. 1955.

*TRADE-MARK

WALLACE LABORATORIES, *New Brunswick, N. J.*

"Much better– thank you, doctor"

Proven in research

1. Highest tetracycline serum levels
2. Most consistently elevated serum levels
3. Safe, physiologic potentiation (with a natural human metabolite)

And now in practice

4. More rapid clinical response
5. Unexcelled toleration

COSA-TETRACYN*

GLUCOSAMINE-POTENTIATED TETRACYCLINE

CAPSULES
(black and white)
250 mg., 125 mg.
(for pediatric or long-term therapy)

ORAL SUSPENSION
(orange-flavored)
125 mg. per tsp. (5 cc.)
2 oz. bottle

NEW! PEDIATRIC DROPS
(orange-flavored) 5 mg. per drop, calibrated dropper,
10 cc. bottle

COSA-TETRASTATIN*

glucosamine-potentiated tetracycline with nystatin

Antibacterial plus added protection against monilial super-infection

CAPSULES (black and pink) 250 mg. Cosa-Tetracyn (with 250,000 u. nystatin)

ORAL SUSPENSION 125 mg. per tsp. (5 cc.) Cosa-Tetracyn (with 125,000 u. nystatin), 2 oz. bottle

COSA-TETRACYDIN*

glucosamine-potentiated tetracycline-analgesic-antihistamine compound

For relief of symptoms and malaise of the common cold and prevention of secondary complications

CAPSULES (black and orange)—each capsule contains: Cosa-Tetracyn 125 mg.; phenacetin 120 mg.; caffeine 30 mg.; salicylamide 150 mg.; buclizine HCl 15 mg.

REFERENCES: 1. Carlozzi, M.: Antibiotic Med. & Clin. Therapy 5:146 (Feb.) 1958. 2. Welch, H.; Wright, W. W., and Staffa, A. W.: Antibiotic Med. & Clin. Therapy 5:52 (Jan.) 1958. 3. Marlow, A. A., and Bartlett, G. R.: Glucosamine and leukemia, Proc. Soc. Exp. Biol. & Med. 84:41, 1953. 4. Shalowitz, M.: Clin. Rev. 1:25 (April) 1958. 5. Nathan, L. A.: Arch. Pediat. 75:251 (June) 1958. 6. Cornbleet, T.; Chesrow, E., and Barsky, S.: Antibiotic Med. & Clin. Therapy 5:328 (May) 1958. 7. Stone, M. L.; Sedlis, A., Bamford, J., and Bradley, W.: Antibiotic Med. & Clin. Therapy 5:322 (May) 1958. 8. Harris, H.: Clin. Rev. 1:15 (July) 1958.

Pfizer *Science for the world's well-being* *Trademark

PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc., Brooklyn 6, New York.*

IN STRESS CONDITIONS SUCH AS:

Spontaneous abortion
Inflammatory diseases
Infectious diseases
Cardiovascular diseases
Metabolic diseases

CAPILLARY AND VASCULAR DAMAGE ARE COMMON FINDINGS

In these stress conditions whether caused by nutritional deficiencies, environment, drugs, chemicals, toxins, virus or infections

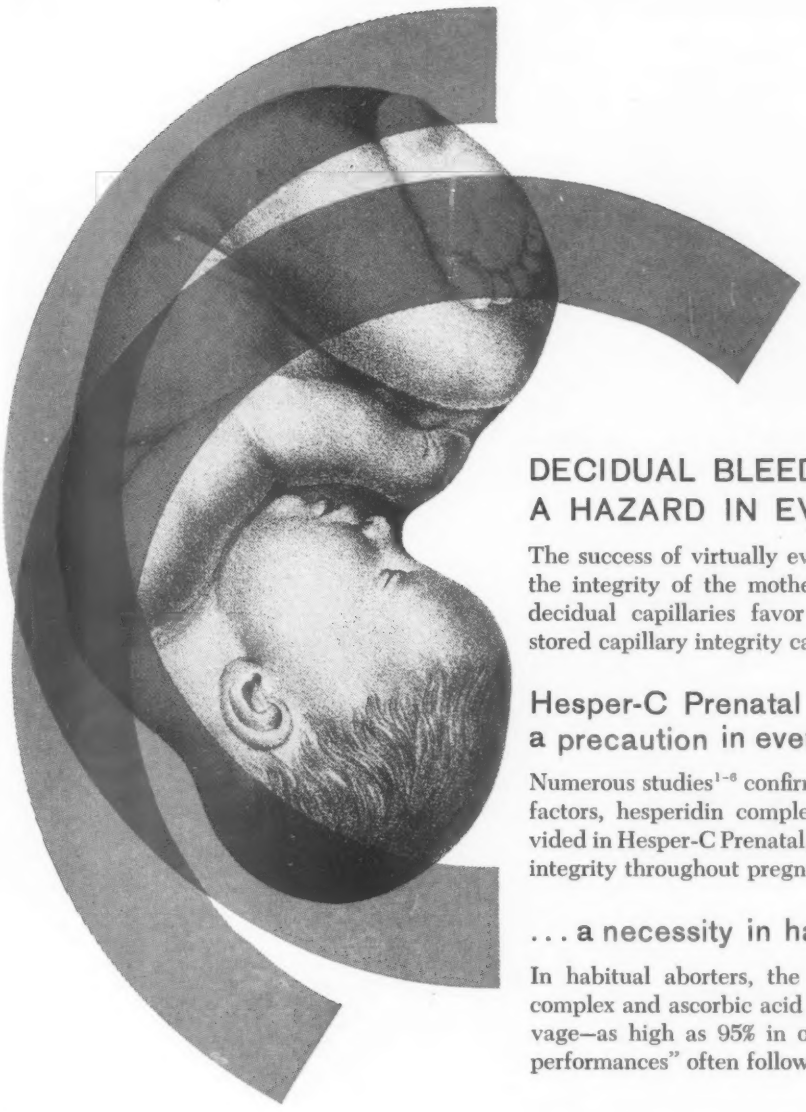
HESPERIDIN, HESPERIDIN METHYL CHALCONE or LEMON BIOFLAVONOID COMPLEX

are indicated as therapeutic adjuncts for the control and management of the associated capillary and vascular damage.

Sunkist and Exchange Brand Hesperidin and Lemon Bioflavonoid Complex are available to the medical profession in specialty formulations developed by leading pharmaceutical manufacturers.

Sunkist Growers

PRODUCTS DEPARTMENT
PHARMACEUTICAL DIVISION
ONTARIO, CALIFORNIA



DECIDUAL BLEEDING . . .
A HAZARD IN EVERY PREGNANCY

The success of virtually every pregnancy depends upon the integrity of the mother's placental vessels: Fragile decidual capillaries favor spontaneous abortion;[1,2] restored capillary integrity can prevent it.

Hesper-C Prenatal . . .
a precaution in every pregnancy

Numerous studies[1-6] confirm that the capillary-protective factors, hesperidin complex and ascorbic acid, as provided in Hesper-C Prenatal, restore and maintain capillary integrity throughout pregnancy.

. . . a necessity in habitual abortion

In habitual aborters, the administration of hesperidin complex and ascorbic acid results in impressive fetal salvage—as high as 95% in one Hesper-C series.[4] "Repeat performances" often follow.

Hesper-C Prenatal

capillary-protective factors + vitamins and minerals

References: 1. Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953. 2. Pearse, H. A., and Trisler, J. D.: Clin. Med. 4:1081, 1957. 3. Javert, C. T.: Spontaneous and Habitual Abortion, New York, The Blakiston Division, McGraw-Hill Book Co., Inc., 1957, p. 338 ff. 4. Javert, C. T.: Obst. & Gynec. 3:420, 1954. 5. Dill, L. V.: M. Ann. District of Columbia 23:667, 1954. 6. Greenblatt, R. B.: Ann. New York Acad. Sc. *61*:713, 1955.

Products of Original Research

THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

HCP 1806/58

Eradicate Infection and Restore Normal Vaginal Flora...

New-'Neosporin'® brand Vaginal Suppositories

Trichomonacidal • Bactericidal

Each suppository contains:

'Aerosporin'® brand Polymyxin B Sulfate	20,000 Units
Neomycin Sulfate	5 mg.
Acetarsone	250 mg.
Beta-lactose	q.s. (approx. 1 Gm.)

In a base containing a surface active agent
Foil-wrapped—Box of 12

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

HE NEEDN'T BE HIGH-STRUNG

WEIGHT REDUCTION: Obese patients may resist dieting because they fear losing the emotional security often involved in overeating. **AMBAR** helps them hold the diet line by giving them a more alert, brighter outlook. **WITHOUT JITTERS:** Methamphetamine, a potent **CNS** augmenter, produces less cardiovascular effect than amphetamine. In **AMBAR** it is combined with just enough phenobarbital to prevent overstimulation. **AMBAR EXTENTABS** provide 10-12 hours of appetite suppression in one controlled-release, extended-action tablet: methamphetamine hydrochloride, 10.0 mg.; phenobarbital (1 gr.) 64.8 mg. **AMBAR TABLETS** for conventional dosage or intermittent therapy contain methamphetamine hydrochloride, 3.33 mg.; phenobarbital (½ gr.) 21.6 mg. **A. H. ROBINS COMPANY, INC.**, Richmond, Virginia, Ethical Pharmaceuticals of Merit Since 1878

WEIGHT REDUCTION WITHOUT JITTERS AMBAR™ Robins

methamphetamine and phenobarbital
TABLETS AND EXTENTABS®

Now available
NEW AMBAR #2
EXTENTABS
(METHAMPHETAMINE 15 mg., PHENOBARBITAL 1 gr.)
for patients who
require higher
methamphetamine
dosage

IN THREATENED
OR HABITUAL ABORTION...
MORE FULL TERM PREGNANCIES...

ENOVID®

...SIMULATES CORPUS LUTEUM HORMONES, thereby
...SUPPORTS THE ENDOMETRIUM, hence
...SUSTAINS FETAL LIFE

Enovid, through its pronounced progesterone-like action and its lesser estrogenic action, enhanced by the addition of ethynylestradiol 3-methyl ether, mimics the action of the corpus luteum hormones.

In *threatened abortion,* due to an endocrine failure to support the hypertrophied endometrium of pregnancy, the potent progesterone-like activity of Enovid is of value.

In *habitual abortion,* resulting from inadequate corpus luteum activity, Enovid supports the decidual endometrium and therefore encourages continuation of the pregnancy.

Each 10-mg. tablet of Enovid contains 9.85 mg. of norethynodrel, a new synthetic steroid, and 0.15 mg. of ethynylestradiol 3-methyl ether.

DOSAGE IN THREATENED ABORTION

Two or three tablets daily on appearance of symptoms. This dosage may be reduced to one or two tablets daily when symptoms disappear. The reduced dosage should be continued to term and an increased dose given if symptoms reappear.

DOSAGE IN HABITUAL ABORTION

One or two tablets daily as soon as pregnancy is diagnosed and continued without interruption at least through the fifth month. Enovid may be safely continued to term if desired.

ENOVID Oral Synthetic Endometropin

(brand of norethynodrel with ethynylestradiol 3-methyl ether)

SEARLE / *Research in the Service of Medicine.*

G. D. SEARLE & CO., Chicago 80, Illinois

TARGET ACTION

specifically on the large bowel

FOR EASIER ELIMINATION

DORBANE®

(1,8-dihydroxyanthraquinone)

selective peristaltic stimulant

■ smooth, overnight action ■ no griping ■ well tolerated, non-habituating

Available in 75 mg. scored tablets and suspension.

WHERE STOOL SOFTENING IS ALSO INDICATED

DORBANTYL® FORTE

(Dorbane, 50 mg. + dioctyl sodium sulfosuccinate, 100 mg.)*

Double strength capsules for maximum economy and convenience.

DORBANTYL®

(Dorbane, 25 mg. + dioctyl sodium sulfosuccinate, 50 mg.)*

For lower dosage and in children.

Available in capsules and suspension.

***In proportions proved optimal by clinical trial.**

(Marks, M. M.: Clin. Med. 4:151, 1957)

SCHENLABS PHARMACEUTICALS, INC., NEW YORK 1, N.Y.

Manufacturers of NEUTRAPEN® for penicillin reactions.

®TRADEMARKS REG. U.S. PAT. OFF. DORBANTYL FORMULA PATENTED. 58158

SchenLabs

in vaginitis

IMPROVED

TRICOFURON®

destroys all 3 *principal pathogens*

Whether vaginitis is caused by Trichomonas, Monilia or Hemophilus vaginalis—alone or combined—TRICOFURON IMPROVED swiftly relieves symptoms and malodor, and achieves a truly high percentage of cultural cures, frequently in 1 menstrual cycle. TRICOFURON IMPROVED provides: a *new* specific moniliacide MICOFUR® brand of nifuroxime, the *established* specific trichomonacide FUROXONE® brand of furazolidone and the *combined* actions of both against Hemophilus vaginalis.

1. *Office* insufflation once weekly of the Powder (MICOFUR [*anti*-5-nitro-2-furaldoxime] 0.5% and FUROXONE 0.1% in an acidic water-soluble powder base). **2.** Continued *home* use twice daily, with the Suppositories (MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base).

Rx NEW BOX OF 24 SUPPOSITORIES WITH APPLICATOR FOR MORE PRACTICAL AND ECONOMICAL THERAPY.

NITROFURANS—a *new* class of antimicrobials—neither antibiotics nor sulfonamides.

EATON LABORATORIES, NORWICH, NEW YORK

in toxemia
of
pregnancy

Diamox*

ACETAZOLAMIDE LEDERLE

nonmercurial
diuretic

DIAMOX effectively produces weight loss through fluid loss in pregnant patients with visible or occult edema, pre-eclampsia, hypertensive disease, and decompensated heart disease.[1]

DIAMOX was administered to 106 pregnant patients, on regular or prescribed diets. The majority were ambulatory and all either had more than the normal amount of visible edema and/or gained more than the average of 1 kg. per week. Response with DIAMOX showed that edema fluid can be removed effectively: 500-2000 Gm. in 24-72 hours, and as much as 11 kg. within 7 days.

A highly versatile diuretic, DIAMOX is particularly advantageous in prenatal management. Lack of taste, ease of administration, and lack of renal and gastrointestinal irritation make its use simple and relatively free of complications.

Supplied: Scored tablets of 250 mg.; Syrup containing 250 mg. per 5 cc. teaspoonful; Ampuls of 500 mg. for parenteral use.

1Dieckmann, W. J.; Harrod, J., and Monardo, A.: The Treatment of Pre-eclamptic Edema with Acetazolamide (Diamox). *Am. J. Obst. & Gynec.* 73:789-800, 1957.

*Reg. U.S. Pat. Off.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N.Y.

This tranquilizer does not affect autonomic balance

DURING PREGNANCY

Miltown therapy resulted in complete relief from symptoms in 88% of pregnant women complaining of insomnia, anxiety, and emotional upsets.*

Miltown (usual dosage: 400 mg. q.i.d.) relieves *both* mental and muscular tension, and alleviates somatic symptoms of anxiety and fear. Miltown *can be used with safety throughout pregnancy.**

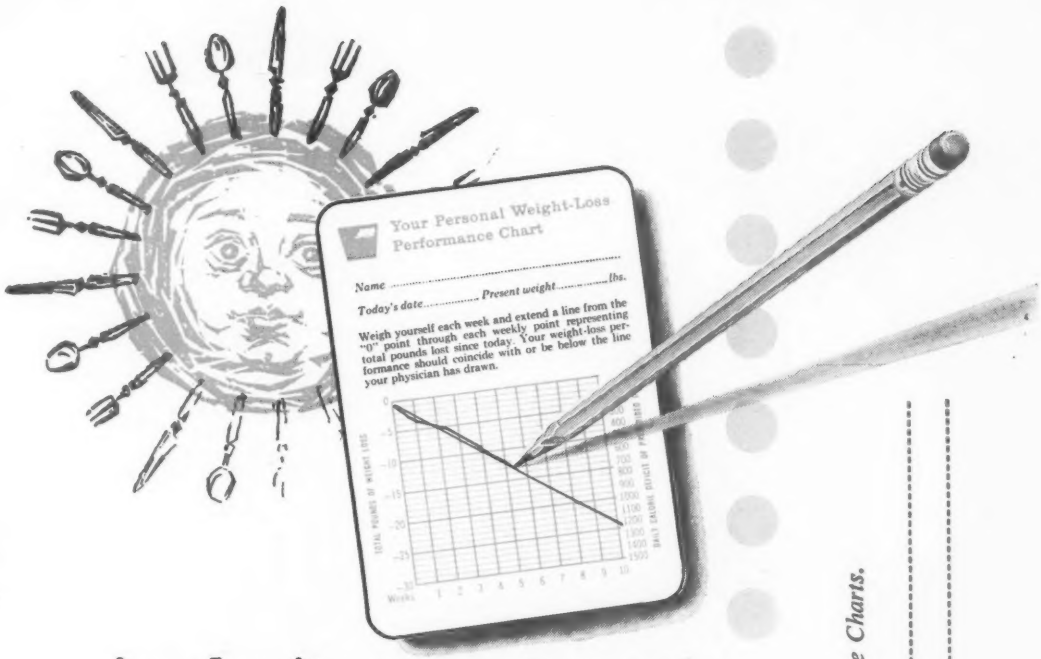
Miltown®

meprobamate (Wallace)

WALLACE LABORATORIES, *New Brunswick, N. J.*

CM-7219

*Belafsky, H. A., Breslow, S. and Shangold, J. E.: *Meprobamate in pregnancy.* Obst. & Gynec. 9:703, June 1957.


Your Personal Weight-Loss Performance Chart
Name .....
Today's date..... Present weight .....lbs.
Weigh yourself each week and extend a line from the "0" point through each weekly point representing total pounds lost since today. Your weight-loss performance should coincide with or be below the line your physician has drawn.

in obesity management ...the incentive plan

YOUR PATIENT CHARTS HIS OWN PERFORMANCE LINE against your PREDICTION LINE

In giving each patient his ten-week chart of predicted weight-loss, you provide weekly goals as incentives for adhering strictly to your prescribed diet.

As the patient records his weight-loss performance week by week on the same chart, he experiences the satisfaction of achieving these goals you have set. And, equally important, he quickly sees the consequences of caloric overindulgence.

Each packet of ten charts includes a calorie nomogram – a time-saver in determining predicted weight-loss on the reducing diet you prescribe.

Exclusively for physicians – A professional service of the

Florida Citrus Commission

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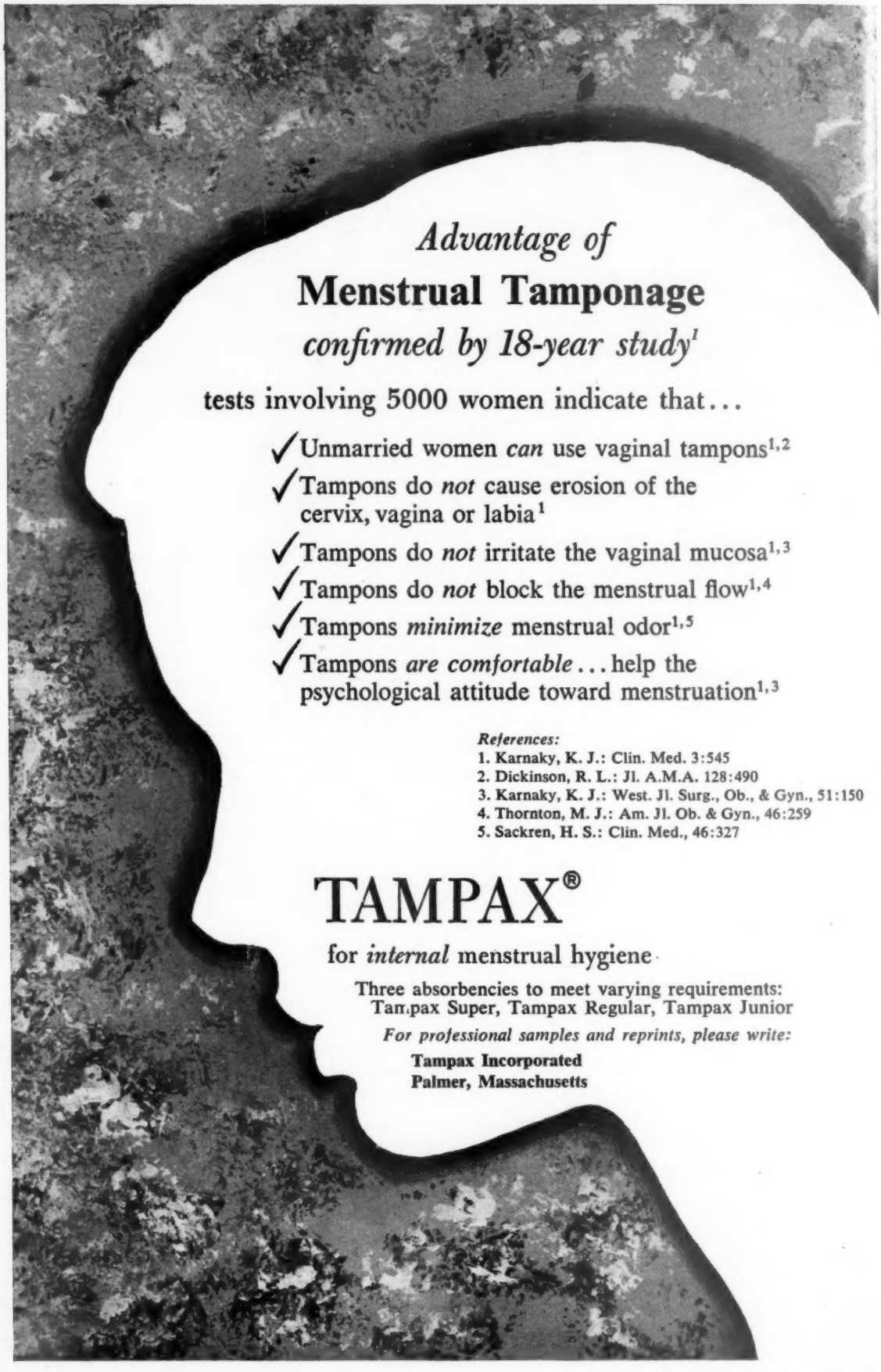
Florida Citrus Commission • Lakeland, Florida

Please send me complimentary packet of ten Weight-Loss Performance Charts.

Name.....

Address.....

City.....*Zone*.....*State*.....


Advantage of
Menstrual Tamponage
confirmed by 18-year study[1]
tests involving 5000 women indicate that...
✓Unmarried women *can* use vaginal tampons[1,2]
✓Tampons do *not* cause erosion of the cervix, vagina or labia[1]
✓Tampons do *not* irritate the vaginal mucosa[1,3]
✓Tampons do *not* block the menstrual flow[1,4]
✓Tampons *minimize* menstrual odor[1,5]
✓Tampons *are comfortable*... help the psychological attitude toward menstruation[1,3]
References:
1. Karnaky, K. J.: Clin. Med. 3:545
2. Dickinson, R. L.: Jl. A.M.A. 128:490
3. Karnaky, K. J.: West. Jl. Surg., Ob., & Gyn., 51:150
4. Thornton, M. J.: Am. Jl. Ob. & Gyn., 46:259
5. Sackren, H. S.: Clin. Med., 46:327
TAMPAX®
for *internal* menstrual hygiene
Three absorbencies to meet varying requirements:
Tampax Super, Tampax Regular, Tampax Junior
For professional samples and reprints, please write:
Tampax Incorporated
Palmer, Massachusetts

no better way to control vomiting

Trilafon Repetabs

perphenazine

1 REPETAB 8 mg.* *Stat.*

repeat in 12 hours

if necessary

documented effectiveness and safety in

gastroenteritis
acute infections
drug-induced vomiting
pre- or postoperative emesis
morning sickness
hyperemesis gravidarum
radiation sickness
carcinomatosis
psychogenic vomiting

when oral therapy is not feasible

TRILAFON Injection

TRILAFON® REPETABS,® 8 mg.—4 mg.
in the outer layer for *prompt effect*
and 4 mg. in the inner core for
prolonged action.

TRILAFON Injection: 5 mg.
ampul of 1 cc.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

Schering

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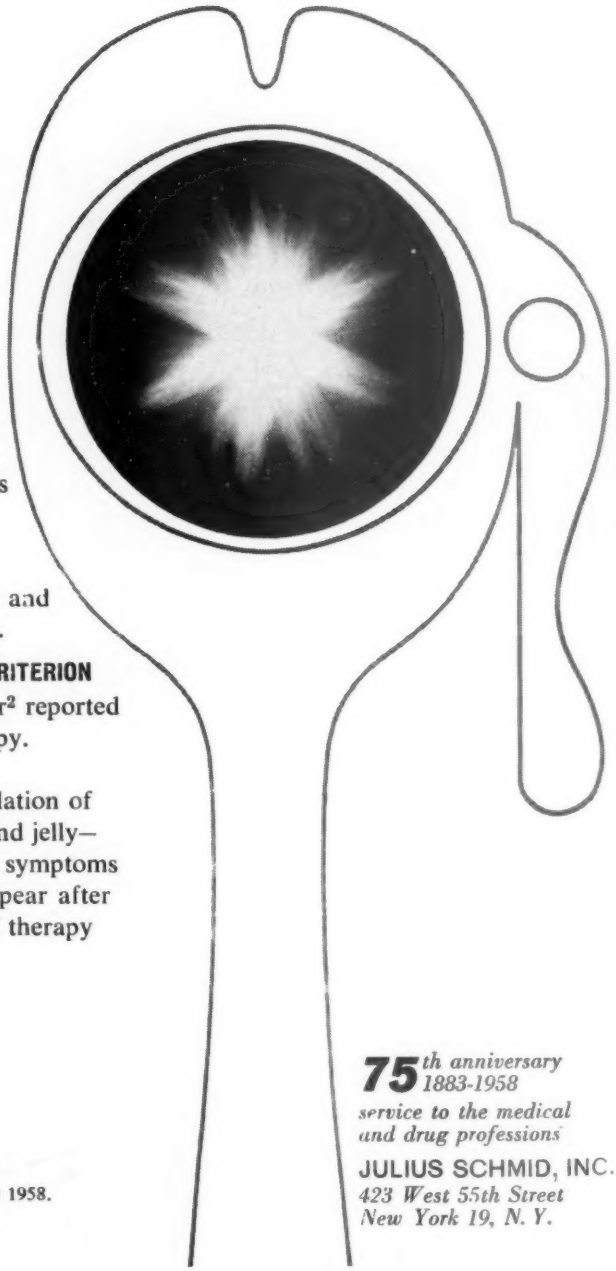
97% clinical success following **explosion** of trichomonads



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References: 1. Decker, A.: New York J. Med. *57*:2237 (July 1) 1957. 2. Weiner, H. H.: Clin. Med. *5*:25 (Jan.) 1958. 3. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955.

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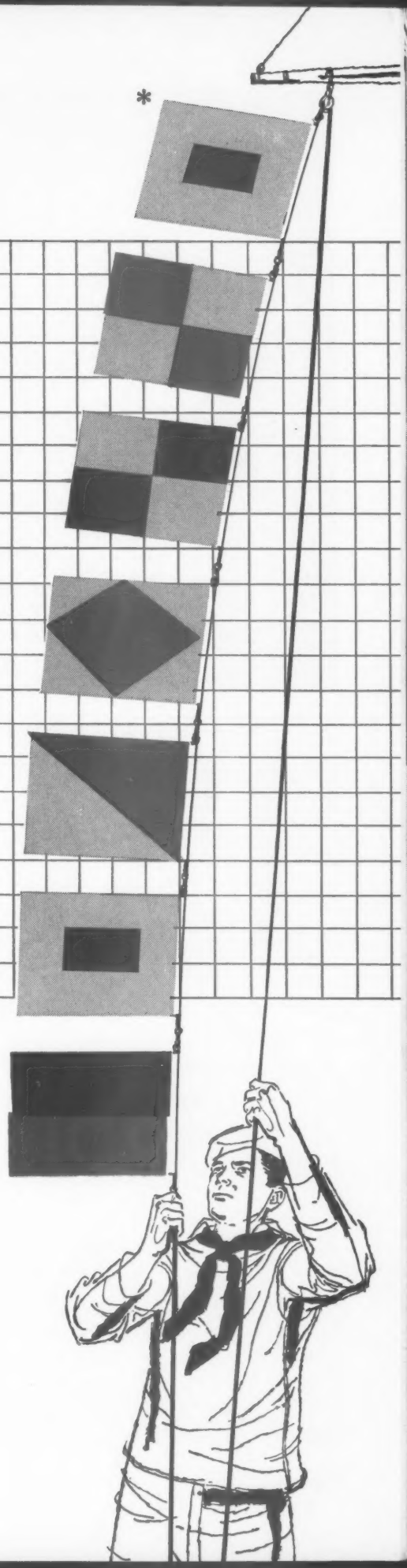

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1. Nulsen, R. O. et al.: Am. J. Obst. & Gynec. 65:1048, 1953. 2. Nulsen, R. O.: Concurrent administration of TACE and Ergonovine, Ohio State M. J. *(in press)*. 3. Bennet, E. T. and McCann, E. C.: J. Maine Med. Assoc. 45:225, 1954. 4. Eichner, E. et al.: Obst. & Gynec. 6:511, 1955.

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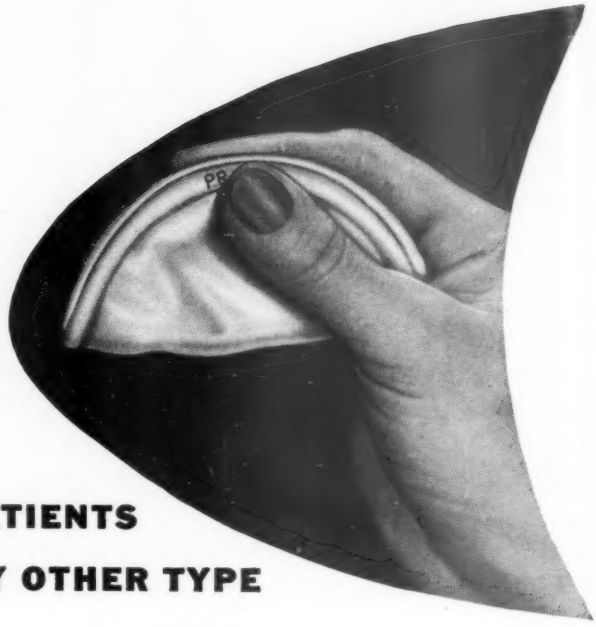

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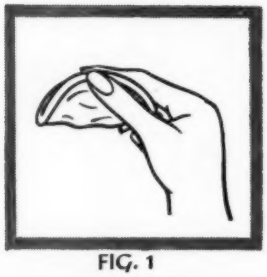

FIG. 1

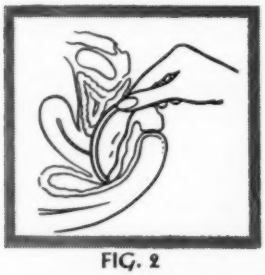

FIG. 2

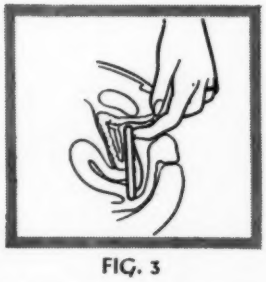

FIG. 3

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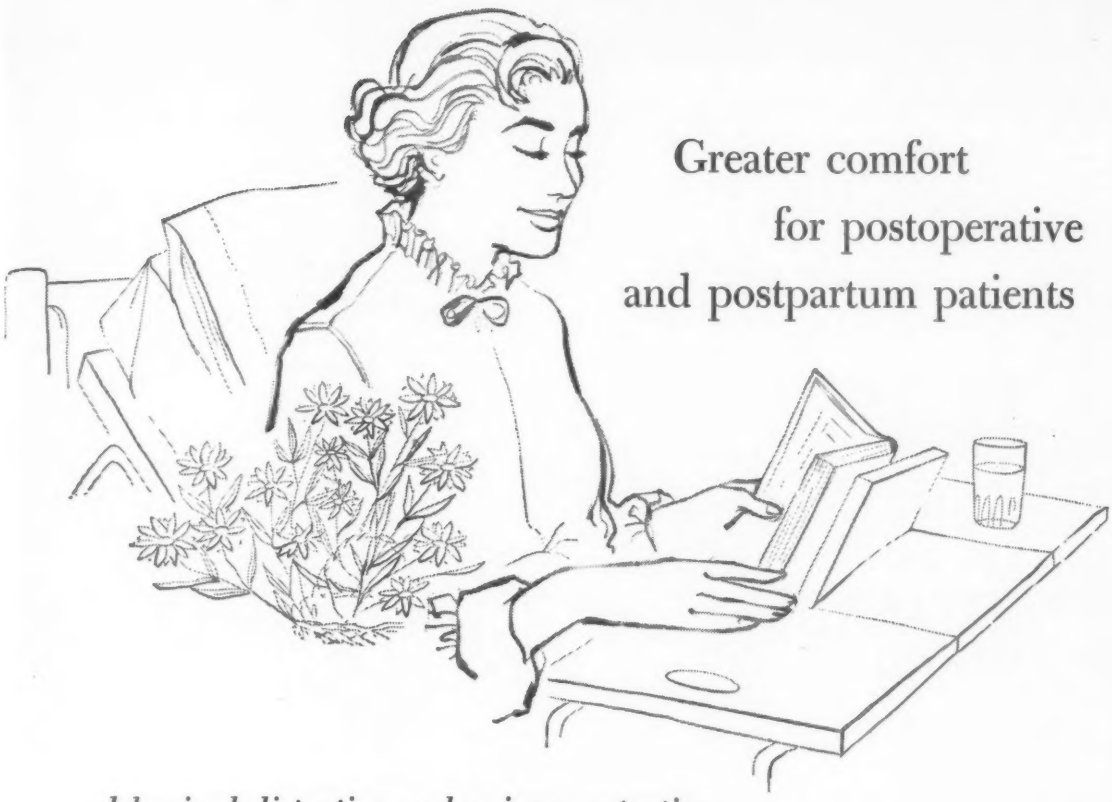

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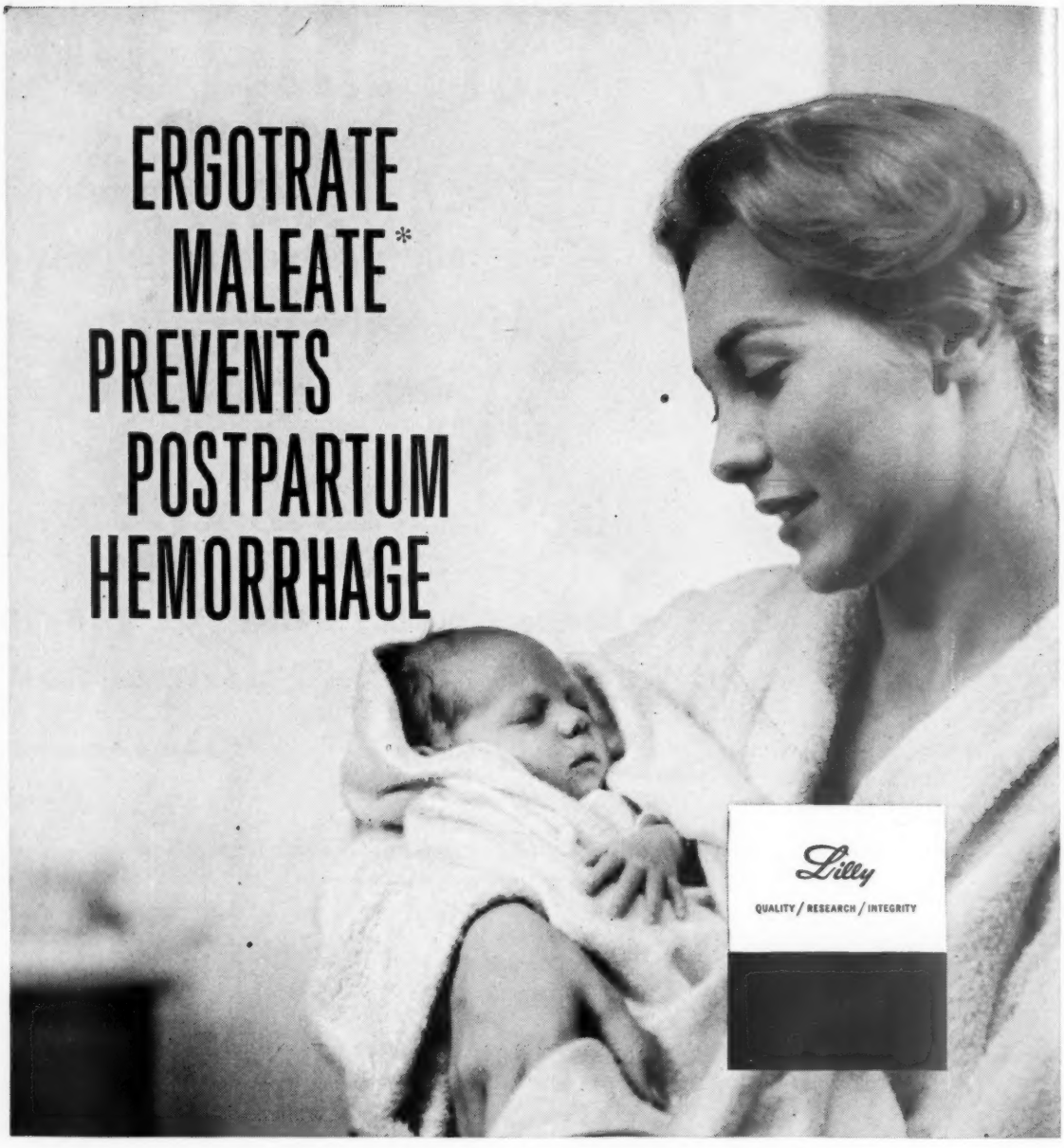

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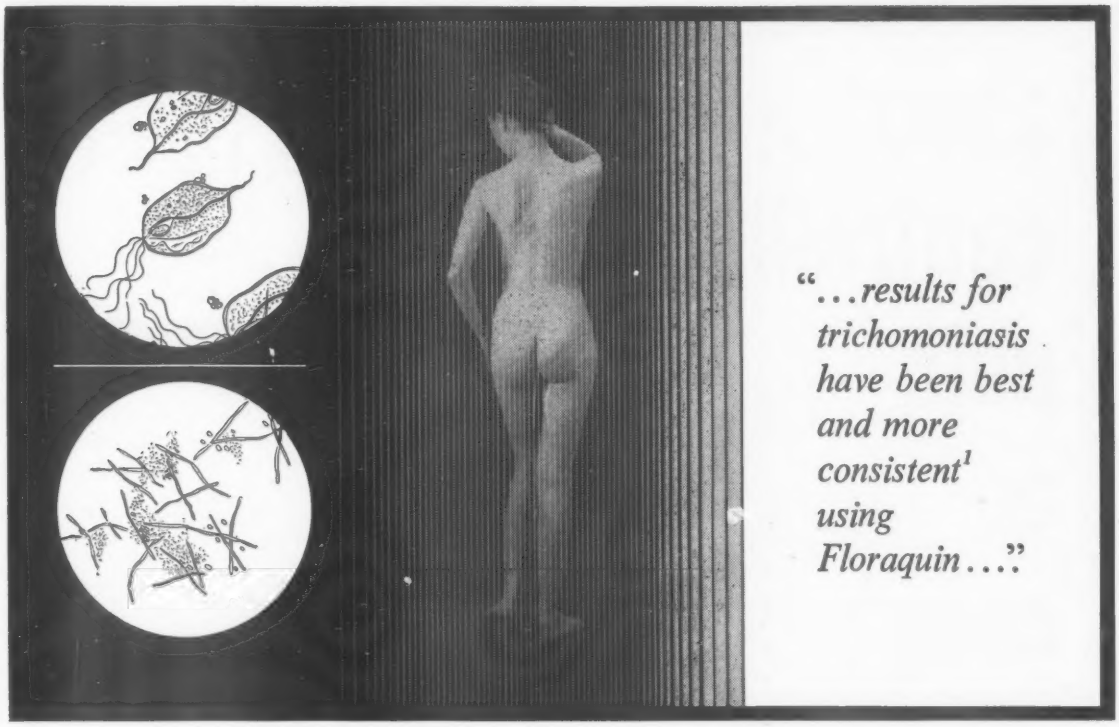

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1. Pitt, M. B.: Leukorrhea. Causes and Management, J. M. A. Alabama *25*:182 (Feb.) 1956.
2. Parker, R. T.; Jones, C. P., and Thomas, W. L.: Pruritus Vulvae, North Carolina M. J. *16*:570 (Dec.) 1955.

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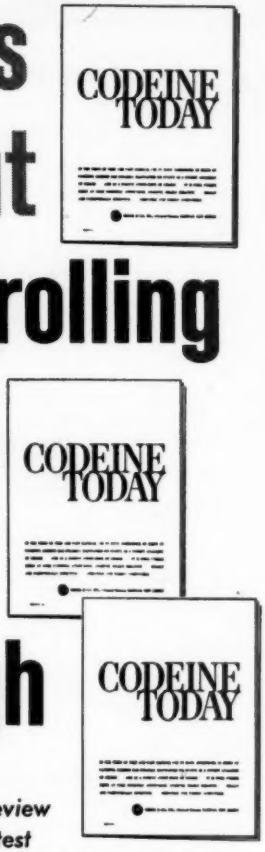

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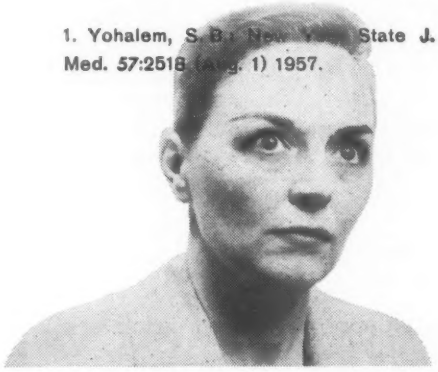
1. Yohalem, S. B.: New York State J. Med. *57*:2518 (Aug. 1) 1957.



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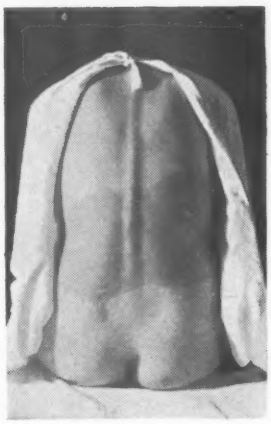

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*L. O. Randall and J. Selitto, *J. Am. Pharm. Assn. (Sc. Ed.)*, 47:313, 1958.

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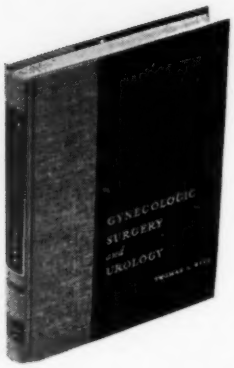

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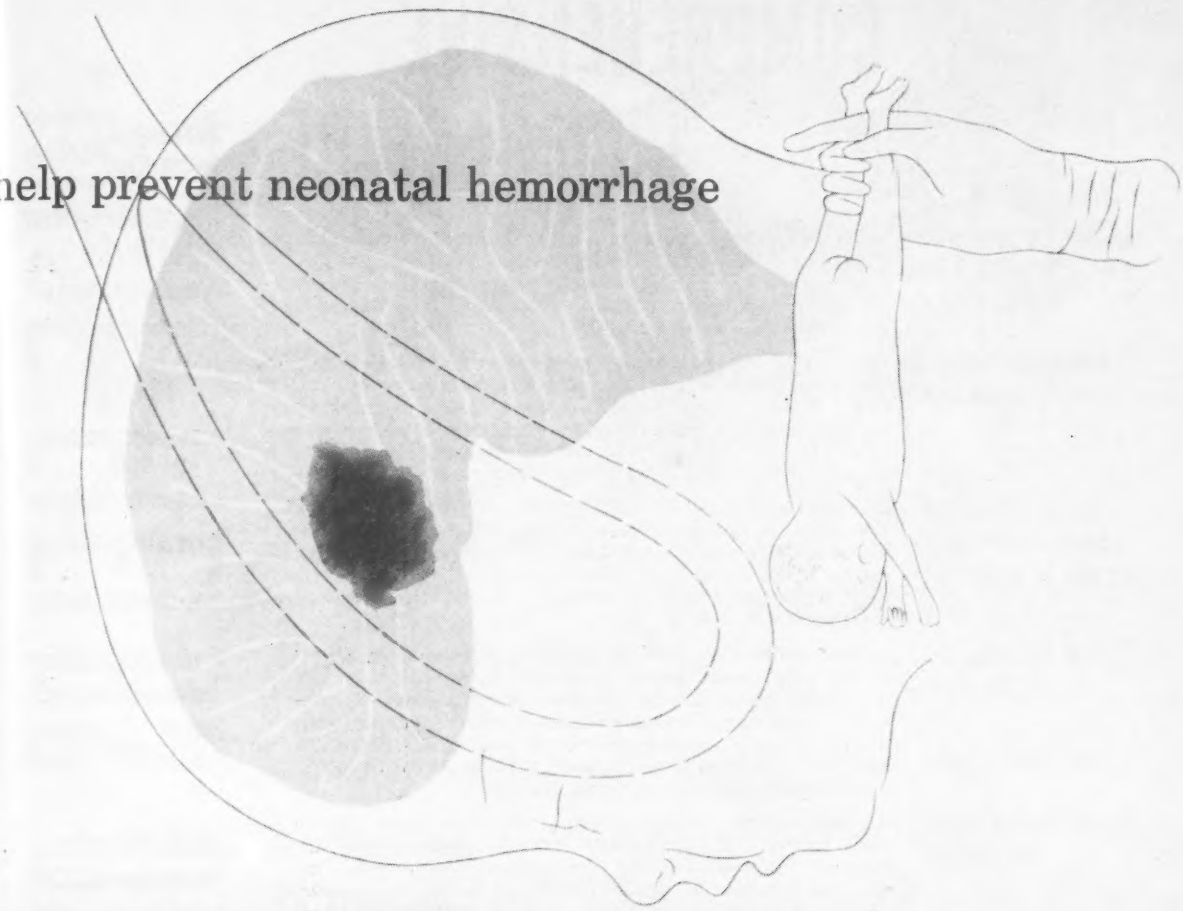

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*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1958, p. 620.

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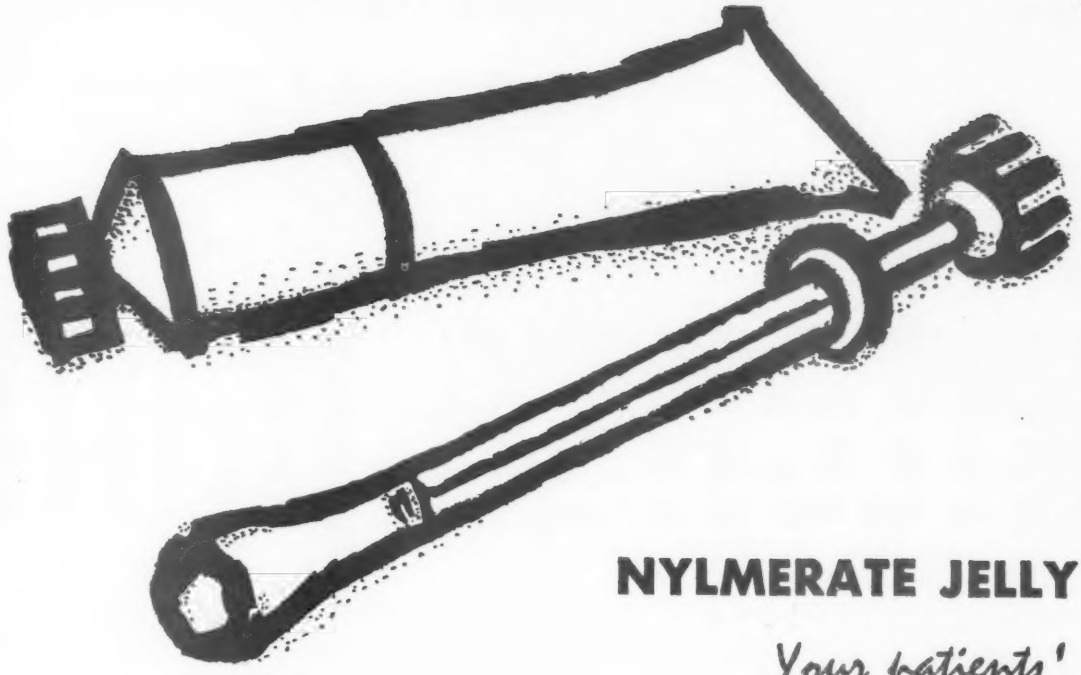

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Vol. XXIX, Fasc. II CONTENTS **October, 1958**

Escobar del Rey, F., and Morreale de Escobar, G.: Studies on the peripheral disappearance of thyroid hormone. IV. The effect of 2,4 dinitrophenol on the I^{131} distribution in thyroidectomized, l-thyroxine maintained rats, 24 hours after the injection of I^{131} labeled l-thyroxine ---- 161

Escobar del Rey, F., and Morreale de Escobar, G.: Studies on the peripheral disappearance of thyroid hormone. V. The effect of 2,4 dinitrophenol on the variations of the I^{131} distribution pattern with time, after injection of I^{131} labeled l-thyroxine into thyroidectomized, l-thyroxine maintained rats ---- 176

Burgers, A. C. J., Leemreis, W., Dominiczak, T., and van Oordt, G. J.: Inhibition of the action of intermedine by lysergic acid diethylamide (LSD 25) in the toad, *Xenopus laevis* ---- 191

Bergstrand, C. G., Ekengren, K., Filipsson, R., and Huggert, A.: Pseudohypoparathyroidism. Familial incidence and comparison with idiopathic hypoparathyroidism ---- 201

Eik-Nes, K. B., and Brizzee, K. R.: Some aspects of corticotrophin secretion in the trained dog. I. The presence of a corticotrophin releasing factor in the blood stream of dogs shortly after hypophysectomy ---- 219

Salvesen, S., and Nissen-Meyer, R.: Effect of meprobamate therapy on the estimation of 17-ketosteroids and 17-ketogenic steroids ---- 224

Holzbauer, M., and Vogt, M.: The release of corticotrophin during severe stress in the rat treated with pentobarbitone and morphine ---- 231

Huis in 't Veld, L. G., and van der Spek, P. A. F.: The effect of 17α-methyl-19-nortestosterone on the excretion of neutral 17-ketosteroids and 17-hydroxy-corticosteroids in in adult males ---- 238

Boseila, A.-W. A.: Influence of cortisone on the basophil granulocytes and the total white cell count in rabbit blood ---- 253

Comsa, J., and Bezssonoff, N. A.: Preparation and bioassay of a purified thymus extract 257

Härtel, G.: Über die Bedeutung der Schilddrüse für das Auftreten von erhöhten Serumcholesterinwerten bei Ratten nach Fütterung von N_1-sulfanilyl-N_2-n-butyl-carbamid (BZ 55) ---- 267

Boseila, A.-W. A., and Moltke, E.: Influence of l-thyroxine on the circulating basophil leucocytes in rabbit ---- 273

de Waard, F.: On the aetiology of endometrial carcinoma ---- 279

Andersson, E.: Hypophysectomy in disseminated cancer of the breast ---- 295

Talanti, S., Kivalo, E., and Kivalo, A.: The acid phosphatase activity in the hypothalamic magnocellular nuclei of the cow embryo ---- 302

Fletcher, P. E., Litvak, J., and Stanbury, J. B.: The capacity of normal man to deiodinate iodotyrosine ---- 307

Skaug, O. E., Lingjærde, P., and Malm, O. J.: P^{32} uptake in hypophysectomized rats ---- 315

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American Cystoscope Makers, Inc. ---- 52
American Meat Institute ---------- 68
American Sterilizer Company -------- 14
Amfre-Grant, Inc. ---------- 65
Arnar-Stone Laboratories, Inc. -------- 22
Astra Pharmaceutical Products, Inc. 24, 95
Ayerst Laboratories ---------- 25, 56

Borden Company, The ------ Fourth Cover
Burroughts Wellcome & Company (U.S.A.), Inc. ---------- 74

Carnation Company & Subsidiaries ---- 40
Ciba Pharmaceutical Products, Inc. ---- ---------- Second Cover
Ciba Pharmaceutical Products, Inc. 16, 105

Desitin Chemical Company ---------- 54
Doho Chemical Corporation ---------- 57
Dome Chemicals, Inc. ---------- 96

Eaton Laboratories ---------- 30, 31, 78
Ethicon, Inc. ---------- 50

Florida Citrus Commission ---------- 81
Fougera & Company, Inc., E. -------- 46

Holland-Rantos Company ---------- 88, 101

Lakeside Laboratories ---------- 47
Lea & Febiger ---------- 94
Lederle Laboratories Division, American Cyanamid Company ---------- 39, 79
Lilly and Company, Eli ---------- 90
Little, Brown & Company ---------- 108

Massengill Company, The S. E. ------ ---------- Insert between pp. 24 and 25
Massengill Company, The S. E. -------- ---------- Insert between pp. 32 and 33
Massengill Company, The S. E. -------- ---------- Insert between pp. 48 and 49
Mead Johnson & Company ---------- 37, 53
Merck & Company, Inc. ---------- 92
Merck Sharp & Dohme ---------- -------- 33, 34, 35, 36, 60, 61, 89, 99, 102
Merrell Company, The Wm. S. -------- 86
Mutual Benefit Life Insurance Company, The ---------- 15

National Drug Company, The 55, 64, 73, 107
National Foundation for Asthmatic Children ---------- 92
Organon, Inc. ---------- 5
Ortho Pharmaceutical Corporation ---- 13

Parke, Davis & Company ---------- 44, 45
Pfizer Laboratories, Div. Chas. Pfizer & Co., Inc. ---------- 28, 70, 71
Poythress & Company, Inc., Wm. P. --- 92

Riker Laboratories ---------- 32
Robins Company, Inc., A. H. ---------- 75
Roche Laboratories, Div. of Hoffmann-La Roche, Inc. ---------- 21, 97
Roussel Corporation ---------- 26, 27

Schenlabs Pharmaceuticals, Inc. ------ 77
Schering Corporation ---------- 83
Schmid, Inc., Julius ---------- 84
Searle & Company, G. D. -- 9, 42, 58, 76, 91
Smith Kline & French Laboratories ---- ---------- 3, 17, 38, 49, 87
Squibb & Sons, E. R. ---------- 12, 66
Sunkist Growers ---------- 72

Tailby-Nason Company, Inc. ---------- 59
Tampax Incorporated ---------- 82

Walker Laboratories, Inc. ---------- 110
Wallace Laboratories ---- 19, 23, 51, 69, 80
Warner Chilcott Laboratories 7, 41, 103, 108
Webster Company, The William A. ---- ---------- Third Cover
Westwood Pharmaceuticals ---------- 11
White Laboratories ---------- 18, 62, 63
Whittaker Laboratories, Inc. ---------- 108
Winthrop Laboratories ---------- 48
Wyeth Laboratories -- 20, 29, 43, 67, 85, 93

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